Exhibit 1

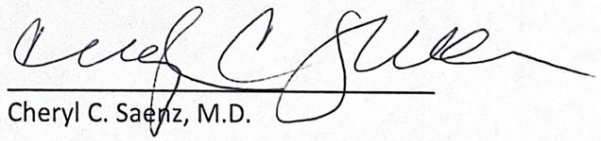
IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF NEW JERSEY

IN RE: JOHNSON & JOHNSON TALCUM POWDER PRODUCTS MARKETING, SALES PRACTICES AND PRODUCTS LIABILITY LITIGATION *THIS DOCUMENT RELATES TO ALL CASES*	MDL NO. 16-2738 (FLW) (LHG)

AMENDED EXPERT REPORT OF CHERYL C. SAENZ, M.D.

Date: May 21, 2024



Cheryl C. Saenz, M.D.

Background and Qualifications

My name is Cheryl Christine Saenz, MD and I am a Clinical Professor in the Department of Obstetrics, Gynecology and Reproductive Sciences at the University of California, San Diego. I have been an attending physician at UC San Diego Health System for 25 years, beginning my employment in October 1998. My current academic appointment is as a clinical professor of gynecologic oncology, and in that role, I serve as an educator, a clinician and a researcher.

As an educator, I am responsible for teaching fellows, residents and medical students about all aspects of gynecologic malignancies, including their epidemiology, risk factors for development, histopathology and pathophysiology, prevention, diagnosis and treatment. All levels of learners actively participate in my clinical practice in the operating room and the clinic, caring for women diagnosed with and known to be at risk for the development of gynecologic malignancies.

As a clinician, I perform surgical procedures and prescribe chemotherapy and immunotherapy for my patients with reproductive cancers. I have a robust clinical practice, as on average, I care for 40-50 patients per week in the clinics and operate on 4-5 patients per week. My patients are typically women with known gynecologic malignancies or known to be at significant risk of developing a gynecologic malignancy. I develop long-term relationships with most of my patients and their families, as they stay in follow-up with me from the time of diagnosis until they are either cured, or unfortunately succumb to their disease. In patients whose cancer recurs, this typically happens within five years of diagnosis, and for those whose cancers do not recur, we consider them to be cured at the five-year landmark. At this juncture, we usually transition our patients into a Survivorship program. To help ensure that the gynecologic cancer care we deliver at UC San Diego Health System is up to date and consistent with national guidelines, we maintain a weekly multi-disciplinary Treatment Planning Conference for the gynecologic oncology service, and I have served as the medical director of that conference for the past 25 years. Additionally, I served as the Chair of the Cancer Committee at the Moores UCSD Cancer Center for a tenure of twelve years. Under my direction, our cancer care program consistently achieved accreditation from the Commission on Cancer, a program of the American College of Surgeons, and was recognized for providing comprehensive, high-quality and multidisciplinary patient-centered care. This accreditation was an integral component in the Moores UCSD Cancer Center selectively achieving National Cancer Institute (NCI)-designated "Comprehensive Cancer Center" status. Only 53 such programs exist in the United States.

I am an active researcher, participating in cooperative group trials and studies investigating new therapeutic options for cancer treatment, and I serve as the primary investigator in investigator-initiated studies at the Moores UCSD Cancer Center. As a member of the Gynecologic Oncology Group, the largest cooperative trials research

group investigating women's cancers, I served on the cervix and vulvar cancer committee and the vaccine subcommittee. One of my most active areas of investigator-initiated research is in the early detection of ovarian cancer. As a result of this work, I have been named the Medical Director of the Strauss Family Center for the Early Detection of Ovarian Cancer. My research in ovarian, cervical and endometrial cancers has been extensively published in such journals as *PNAS*, *Nature Communications*, *Gynecologic Oncology*, *Cancer Research* and *PLoS Biology*.

I attended Cornell University and graduated with a BA in Biopsychology in 1985. I completed my medical school training at the University of California, Irvine and then enrolled in a four-year residency program in Reproductive Medicine at the University of California, San Diego. During this time, I was awarded a Galloway Fellowship at Memorial Sloan Kettering Cancer Center. At the completion of my residency, I was accepted into the board-eligible fellowship in Gynecologic Oncology at Memorial Sloan Kettering Cancer Center and completed my training in 1998. I was initially boarded in Obstetrics and Gynecology in 1999 and in Gynecologic Oncology in 2001, by the American Board of Obstetrics and Gynecology. I have maintained my certification in both fields, with my most recent recertification being in 2022.

I am a full member of the Society of Gynecologic Oncology and the American Society of Clinical Oncology, a Fellow of the American College of Surgeons and the American Congress of Obstetrics and Gynecology. I received a National Institutes of Health Women's Reproductive Health Research Scholars Fellowship from 2002-2007 and an NCI Clinical Investigator Team Leadership Award from 2010-2012. This award recognizes outstanding investigators whose participation and activities promote successful clinical trial research programs.

I served on the Board of Directors of the Foundation for Women's Cancer from 2007-2013 and as the Chair of that Foundation's Education Committee from 2013-2016. The Foundation for Women's Cancer is the patient advocacy organization that was founded by and is supported by members of the Society of Gynecologic Oncology. It is regarded as one of the most reliable resources for patients with gynecologic cancers. I have served as course director for many ovarian cancer survivors' courses (supported by the Foundation for Women's Cancer and the Society of Gynecologic Oncology). I have contributed to the education of the next generation of women scientists and doctors and promote diversity in these fields by serving as the director for medical education for the BeWise (Better Education for Women in Science and Engineering) Saturday Academy for several years. This is a philanthropically–funded program in San Diego County, which mentors young women from public high school programs and encourages them to pursue careers in science and medicine.

I have been retained as a content expert on bills presented to the California state legislature on ovarian cancer screening and health care coverage for gynecologic cancer screening tests. I am contracted by the Medical Board of California and serve as an

expert reviewer in matters of gynecologic oncology that are under investigation by the Department of Consumer Affairs. I am one of only two gynecologic oncologists asked to fulfill this role by the State of California. As a reviewer, it is my responsibility to critique the quality of care provided to patients that have made formal complaints to the Medical Board and render a judgement as to whether or not that care departs from standard practice and the degree of that departure, if one exists. Promoting a culture of quality improvement and patient safety is something that I regularly pursue through my involvement with the PACE (Physician Assessment and Clinical Education) program at UCSD. The PACE program at UCSD is the largest assessment and remediation program for healthcare professionals in the country and the program collaborates with physicians, state medical boards and hospitals from around the country. I have been involved with the PACE program for over 20 years and serve as the primary assessor for evaluating individuals in the field of gynecologic oncology with respect to their fitness for duty.

My opinions in this report are based upon my education, experience and expertise in the field of Gynecologic Oncology. I also base my opinions on my review of the peer-reviewed published scientific literature. All opinions are stated to a reasonable degree of medical certainty. I am being compensated at a rate of $750 per hour for my work on this matter and $1200 per hour for any time spent testifying at deposition or in court.

Ovarian Cancer – Overview

In the United States, ovarian cancer ranks 6th in cancer deaths in women. It is estimated that 19,680 women will be diagnosed with ovarian cancer and 12,740 women will die from this disease in 2024.[1,2] Over the course of her lifetime, a woman's risk of developing ovarian cancer continues to increase, with an overall estimate of 1.1%. The incidence rate of ovarian cancer has been consistently declining since the 1990s and this decline is attributed, at least in part, to an increased use of oral contraceptives and a decreased use of postmenopausal hormone replacement therapy – both important risk factors in the development of the disease.[3] The median age of diagnosis is 63 years old, with 65% of cases being diagnosed between the ages of 45-74.[4] The most common type of ovarian cancer is epithelial ovarian cancer. Malignant epithelial cells have distinct histologic subtypes, and these include high grade serous (the most common at ~70% and includes cancers that originate from fallopian tube epithelium or from the lining of the abdominal cavity, called primary peritoneal cancer), low-grade serous, mucinous, endometrioid and clear cell carcinoma. Each of these histologic subtypes has a distinct

[1] National Cancer Institute, Surveillance, Epidemiology and End Results Program: *Cancer Stat Facts: Ovarian Cancer* (last accessed May 12, 2024) https://seer.cancer.gov/statfacts/html/ovary.html
[2] American Cancer Society. (2024). Cancer Facts & Figures 2024. *American Cancer Society.*
[3] American Cancer Society. (2024). Cancer Facts & Figures 2024. *American Cancer Society.*
[4] Ovarian Cancer Research Alliance (OCRA): Get the Facts (last accessed May 20, 2024) https://ocrahope.org/get-the-facts/statistics/

molecular profile and chemosensitivity pattern, and each varies in risk factors for development. Nearly all high-grade serous carcinomas are thought to originate from mutations in the *TP53* gene early on in the pathway to malignant transformation. *TP53* is a tumor suppressor gene and mutations can lead to loss of critical cellular functions. Findings of mutations in this gene can be found in the tubes of high-risk women undergoing risk-reducing prophylactic surgery, long before there is clinical or pathologic evidence of invasive cancer cells. These precursor lesions have been termed STIC (serous tubal intraepithelial carcinomas) lesions and their signature p53 mutations can be identified with immunohistochemistry staining.[5,6] Notably in these same women, there is no evidence of acute or chronic inflammation in the tissues adjacent to where these STIC lesions are found.[7]

In general, factors that are well established as increasing a woman's risk of developing ovarian cancer include age, genetics, family history and personal history of cancer, hormone replacement therapy, and reproductive history (including early menarche and late menopause). Other risk factors have been associated with an increased risk of developing specific histologic subtypes of ovarian cancer. These include endometriosis (strongly associated with endometrioid and clear cell carcinoma and to a lesser extent the serous histologic subtype), tobacco use (associated with mucinous carcinoma) and obesity (associated with borderline, endometrioid, clear cell and mucinous carcinomas). Additionally, there are factors that appear to decrease a woman's risk of developing ovarian cancer, and these include use of oral contraceptive agents for at least five contiguous years, tubal ligation, the age at which a woman first gives birth as well as the number of births, breastfeeding for on average six months with each child and surgical removal of the ovaries and tubes. In addition, a large meta-analysis has shown that use of an IUD for contraception results in a reduction in the risk of ovarian cancer by 32%.[8] This is regardless of the type of IUD used (hormonal vs. non-hormonal). The authors hypothesize that it is the chronic inflammatory response induced by the presence of the IUD that confers the anti-carcinogenic benefit and results in fewer cases of ovarian cancer being diagnosed in women who use IUDs.[9] Some authors refer to these factors as "protective," but I do not believe that terminology is appropriate, as these factors cannot prevent the disease, they are simply associated with a reduced risk of development.

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[5] Visvanathan K., et al. Fallopian tube lesions in women at high risk for ovarian cancer: a multicenter study. *Cancer Prevention Research*. 2018 Nov 1;11(11):697-706 (and supplemental materials).
[6] Kuhn E., et al. TP53 mutations in serous tubal intraepithelial carcinoma and concurrent pelvic high-grade serous carcinoma-evidence supporting the clonal relationship of the two lesions. *The Journal of Pathology*. 2012; 226(3):421-6.
[7] Malmberg K., et al. Serous tubal intraepithelial carcinoma, chronic fallopian tube injury, and serous carcinoma development. Virchows Archiv. 2016;468(6):707-713.
[8] Wheeler LJ., et al. Intrauterine Device Use and Ovarian Cancer Risk: A Systematic Review and Meta-analysis. *Obstetrics & Gynecology.* 2019; 134(4):791-800.
[9] Wheeler LJ., et al. Intrauterine Device Use and Ovarian Cancer Risk: A Systematic Review and Meta-analysis. *Obstetrics & Gynecology*. 2019; 134(4):791-800.

Prognosis for patients with epithelial ovarian cancer is heavily dependent upon stage at diagnosis, and unfortunately, the majority of women are diagnosed with advanced stage disease, where recurrences are common. Nonetheless, 5-year survival rates are relatively high at 50.9%, and in 2021, in the United States, approximately 238,484 women were alive who had been diagnosed with ovarian cancer – including those who had been cured of the disease.[10] Because prognosis and prospects for cure are largely dependent upon stage at initial diagnosis, much research has focused on trying to identify effective screening tests for the early detection of ovarian cancer. This research has been challenging, however, as accessing the tissues of the fallopian tube or the ovary, where early lesions are developing, is problematic, unlike cancers of the colon, breast and cervix.

Several hypotheses exist that attempt to explain how each of the established risk factors could ultimately be involved in the causation of ovarian cancer; however, each of these is simply still a hypothesis. The epidemiologic literature can demonstrate associations, but it cannot assign causation, and the cancer biology literature lacks consistent data demonstrating how ovarian cancer is initiated.

Established Risk Factors for the Development of Ovarian Cancer

Age

Age itself is an independent risk factor for the development of ovarian cancer, as it is in most cancers. The majority of epithelial ovarian cancers are diagnosed in women 55-64 years old. As a woman ages, her risk of ovarian cancer continues to increase, peaking in the late 70s. Gates et al. (2010) reported on a 2% per year increase in the risk of developing ovarian cancer in women aged 50 or greater for all of the epithelial histologic subtypes, and the risk rose to 4% per year for the serous subtype in particular.[11] Through mathematical modeling, based on cancer genome sequencing and epidemiologic data, Tomasetti and Vogelstein (2017) found that two-thirds of the mutations in cancers are caused by random DNA replication errors in normal cellular functioning.[12] The longer you live, the more of these unavoidable replication errors will occur, thereby increasing the chances that you will develop cancer as you age, including ovarian cancer.

Genetics

One of the most well-established risk factors for the development of epithelial ovarian cancer is the inheritance of a gene that is mutated in a manner that can predispose a woman to the development of ovarian cancer. The majority (~70%) of these mutations

[10] National Cancer Institute, Surveillance, Epidemiology and End Results Program: *Cancer Stat Facts: Ovarian Cancer* (last accessed May 12, 2024) https://seer.cancer.gov/statfacts/html/ovary.html

[11] Gates MA., et al. Risk factors for epithelial ovarian cancer by histologic subtype. *American Journal of Epidemiology*. 2010; 171:45-53.M

[12] Tomasetti C., Stem cell divisions, somatic mutations, cancer etiology, and cancer prevention. *Science*. 2017; 355(6331):1330-1334.

are found in either BRCA1 or BRCA2, genes that were initially characterized in the mid-1990s. Mutations in these two genes confer homologous recombination deficiency (HRD+), a condition by which cancerous cells have impaired DNR repair mechanisms, making them more sensitive to chemotherapy. Since the characterization of BRCA1 and 2, many other genes that also confer HRD+ status and an inherited increased risk of developing ovarian cancer, have been identified. These genes are often clustered together and referred to as "BRCA-ness" genes, and these account for ~29% of the inherited ovarian cancers.[13] To date, roughly 16 different genes have been identified in this cluster, but new genes are being identified and added to testing panels every year. In the mid-1990s, we only tested for two genes (BRCA1 and 2); by contrast, the expanded panel testing currently available through many commercial labs examines more than 25 different genes. Genes associated with HNPCC (Lynch syndrome) are responsible for the remaining inherited ovarian cancers. These genes have mutations in the mis-match repair pathway, another pathway that decreases a cancer cell's ability to repair errors in DNA replication. It is presently thought that there are still genes yet to be identified that will fall into the "BRCA-ness" category that will ultimately reveal that perhaps as many as 30% of all ovarian cancers are actually linked to inheritance of a loss-of-function mutation. Importantly, many of the women found to have inherited a deleterious mutation have no prior family history of breast or ovarian cancer.[14] And as reported by Eng (2018), when the inherited mutation is being transmitted through the paternal lineage, the cancer risk may appear to "skip" generations, particularly if the mutation has an X-linked pattern of inheritance.[15] The lifetime risk of developing ovarian cancer for a woman who inherited a deleterious mutation varies, as it is dependent upon the individual mutation, but the risk for an inherited mutation in BRCA1 is estimated to be 40-53% and for BRCA2 20-30%.[16] This equates to roughly a 20-50 times higher lifetime risk of developing ovarian cancer than a woman who does not carry such a mutation.

Family and Personal Cancer History

Women with a family history of ovarian cancer (even in the face of negative or absent genetic testing) are at an increased risk of developing ovarian cancer themselves. The lifetime risk of a woman who has a first-degree relative with ovarian cancer is 5%, which is three times higher than an average woman's risk. The risk is even higher if the

[13] Walsh T., et al. Mutations in 12 genes for inherited ovarian, fallopian tube, and peritoneal carcinoma identified by massively parallel sequencing. *Proceedings of the National Academy of Sciences*. 2011; 108(44):18032-7.

[14] Walsh T., et al. Mutations in 12 genes for inherited ovarian, fallopian tube, and peritoneal carcinoma identified by massively parallel sequencing. *Proceedings of the National Academy of Sciences*. 2011; 108(44):18032-7.

[15] Eng K., et al. Paternal lineage early onset hereditary ovarian cancers: A familial ovarian cancer registry study. *PLOS Genetics*. 2018; 14(2): e1007194.

[16] Ramus SJ., et al. The contribution of BRCA1 and BRCA2 to ovarian cancer. *Molecular Oncology*. 2009; 3(2):138-50.

affected relative was <50 years old at the time of diagnosis.[17] Additionally, a family history of breast cancer, colon cancer, rectal cancer and uterine cancer increases a woman's risk of developing ovarian cancer over the background population risk. Any woman who herself has been afflicted by cancer is at an increased risk for developing ovarian cancer. In particular, a personal history of breast cancer, uterine cancer, cervical cancer, thyroid cancer, melanoma, colon or rectal cancer increases the risk of developing ovarian cancer.[18]

Reproductive History, Early Menarche and Late Menopause

It is well established that women who are nulliparous have an increased risk of developing ovarian cancer. Women who have ever given birth appear to have a reduced risk, with each subsequent pregnancy reducing the risk further by 10-20%.[19] The age at which a woman has her first child also appears to influence risk as women who have their first child later in life (>35 years old) appear to have less reduction in risk than those who have their children earlier. Additionally, any woman who has been diagnosed with infertility is at an increased risk of ovarian cancer, and this risk remains whether or not fertility agents were used (which incidentally are not known to be a risk factor).[20,21]

Consistently over the years, early age at menarche and late age at menopause have been associated with an increased risk of developing ovarian cancer. This finding has been interpreted to mean that the higher the number of ovulatory events that occur in a woman's lifetime, the higher her risk of developing ovarian cancer. This led to the incessant ovulation hypothesis of ovarian cancer development. Fathalla first published this hypothesis in 1971, and the theory is that the disruption of the surface epithelium of the ovary that occurs with each ovulatory event creates an inflammatory process that can ultimately lead to malignant transformation in the ovary.[22] The data for the influence of age at menarche seems variable, but the age of menopause data seems more consistent, with each five-year increase in the age of menopause increasing the risk of ovarian cancer by ~6%.[23] Support for the incessant ovulation hypothesis is still lacking, as studies on ovulatory suppression do not entirely account for the magnitude in risk reduction seen with these interventions (e.g., breastfeeding, pregnancy and oral

[17] Webb P et al. Epidemiology of epithelial ovarian cancer. *Best Practice & Research: Clinical Obstetrics & Gynecology*. 2017; 41:3-14.
[18] Hall HI., et al. Second primary ovarian cancer among women diagnosed previously with cancer. *Cancer Epidemiology and Prevention Biomarkers*. 2001; 10(9):995-9.
[19] Wentzensen N., et al. Ovarian cancer risk factors by histologic subtype: an analysis from the Ovarian Cancer Cohort Consortium. *Journal of Clinical Oncology*. 2016; 34(24):2888-98.
[20] Kurta ML., et al. Use of fertility drugs and risk of ovarian cancer: Results from a US-based case-control study. *Cancer Epidemiology and Prevention Biomarkers*. 2012; 21(8), 1282-92.
[21] Venn A., et al. Breast and ovarian cancer incidence after infertility and in vitro fertilisation. *Lancet*. 1995; 346:995-1000.
[22] Fathalla MF. Incessant ovulation-a factor in ovarian neoplasia. *Lancet*. 1971; 2(7716):163.
[23] Wentzensen N., et al. Ovarian cancer risk factors by histologic subtype: an analysis from the Ovarian Cancer Cohort Consortium. *Journal of Clinical Oncology*. 2016; 34(24):2888-98.

contraceptives).[24] For example, a woman who uses oral contraceptives contiguously for 5 years has a 20-50% reduction in her risk of developing ovarian cancer, yet the total number of monthly ovulatory events that are actually suppressed in this time period would be at most 60 events, which is far less than 20-50% of an average woman's lifetime ovulatory events. Thus, the benefit in risk reduction of oral contraceptives is more than just suppressing ovulatory events and any supposed ovulatory-associated inflammatory response, and the actual molecular pathway of that benefit has yet to be determined in the pathogenesis of ovarian cancer. Additionally, Huang and colleagues published a study examining the association between a woman's lifetime ovulatory years (LOY) and levels of systemic inflammatory biomarkers and found an inverse relationship.[25] Specifically, each 5-year increase in LOY was associated with statistically significant lower levels of C-reactive protein (a marker of inflammation) in both premenopausal and postmenopausal women. The authors conclude that their findings do not support elevated systemic inflammation as the underlying mechanism for the association between higher LOY and an increased risk of developing ovarian cancer.

Postmenopausal Hormone Replacement Therapy

Use of postmenopausal hormone replacement therapy has waxed and waned over the years as various studies have reported on the health benefits vs. risks associated with the use of this therapy. Despite this, the use of postmenopausal hormones has consistently been associated with an increased risk of developing ovarian cancer in multiple studies.[26,27,28,29] This is true for both estrogen alone and estrogen in combination with progesterone. Estimates are that the risk increases in the range of 20-40% for five years or more of use, and the risk continues for at least five years, even after the woman stops using the hormone replacement therapy.

Histologic Specific Risk Factors

Endometriosis

Endometriosis has been found to increase a woman's risk of developing ovarian cancer by two- to threefold. The risk seems particularly strong for women who are found to have endometrioid or clear cell histologies; endometrioid adenocarcinomas account for

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[24] Whittemore AS., et al. Characteristics relating to ovarian cancer risk: Collaborative analysis of 12 US case-control studies: IV. Pathogenesis of epithelial ovarian cancer. *American Journal of Epidemiology*. 1992; 136(10):1212-20.

[25] Huang T., et al. Estimated number of lifetime ovulatory years and its determinants in relation to levels of circulating inflammatory biomarkers. *American Journal of Epidemiology.* 2020; 189(7), 660-670.

[26] Collaborative Group on Epidemiological Studies of Ovarian Cancer. Menopausal hormone use and ovarian cancer risk: individual participant meta-analysis of 52 epidemiological studies. *The Lancet*. 2015; 385(9980):1835-42.

[27] Urban N., et al. Identifying post-menopausal women at elevated risk for epithelial ovarian cancer. *Gynecologic Oncology*. 2015; 139(2):253-60.

[28] Ovarian Cancer Research Alliance *Risk Factors* (last accessed May 6, 2024) https://ocrahope.org/patients/about-ovarian-cancer/risk-factors/

[29] American Cancer Society. Cancer Facts & Figures 2024. *American Cancer Society* 2024.

69% of the ovarian malignancies associated with endometriosis, and clear cell carcinomas account for 13.5%.[30] These percentages are far higher than the percentages of these histologies found in ovarian cancers not associated with endometriosis (10-20% and 3-10%, respectively). One study that examined the differential risks of developing ovarian cancer by "type of endometriosis" found that women who had a history of ovarian endometriosis had the greatest risk of ovarian cancer with an SIR of 10.1 (CI 5.50,16.9) for clear cell carcinomas, 4.72 (CI 2.75,7.56) for endometrioid carcinomas and 1.62 (CI 0.99,2.49) for high grade serous carcinoma.[31] The additional finding of cytologic atypia in implants of endometriosis (akin to the precancerous hyperplasia with atypia that precedes the development of endometrial cancer) supports the hypothesis that endometrioid and clear cell carcinomas may undergo a different process of malignant transformation than do serous carcinomas.[32]

Molecular support for this clinical observation is found in a large multi-level investigation into shared genetic relationships between endometriosis and ovarian cancer. Mortlock et al (2022) examined 14,949 cases of endometriosis and 25,509 cases of ovarian cancer and found strong genetic correlations between endometriosis and clear cell and endometrioid histologies, and to a lesser extent, high grade serous carcinomas.[33] The genomic regions that were shared between the endometriosis and each histologic subtype of ovarian cancer varied, arguing that the shared and non-shared components likely give rise to distinct molecular pathways which contribute to the development of the different histotypes of ovarian cancer. A recent publication by Beddows et al. (2024) may have shed some light on how it is determined which genes are activated in endometriosis to distinctly give rise to either the clear cell or endometrioid subtype.[34] These authors performed an RNA transcription analysis and identified that the expression profile of the clear cell cancers resembled normal secretory endometrium, whereas the endometrioid cancers had expression profiles more akin to proliferative endometrium. Additionally, methylation of the estrogen receptor gene was found to be enriched in the clear cell carcinomas, thereby preventing transcription of this gene and "locking" the cells into a secretory state. The authors conclude that it is not solely the cell type of origin that determines the cancer histologic subtype, but also the "state" of the cell in terms of which pathways are expressed.[35]

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[30] Friedlander ML. Prognostic factors in ovarian cancer. *Seminars in Oncology*. 1998; 25(3):305-14.
[31] Saavalainen, L., et al. Risk of gynecologic cancer according to the type of endometriosis. *Obstetrics & Gynecology.* 2018; 131(6), 1095-1102.
[32] Sainz de la Cuesta RS., et al. Histologic transformation of benign endometriosis to early epithelial ovarian cancer. *Gynecologic Oncology*. 1996; 60(2):238-44.
[33] Mortlock, S, et al. A multilevel investigation of the genetic relationship between endometriosis and ovarian cancer histotypes*. Cell Reports Medicine*. 2022;3:100542.
[34] Beddows I, et al. Cell State of Origin Impacts Development of Distinct Endometriosis-Related Ovarian Carcinoma Histotypes. *Cancer Res.* 2024; 84(1):26-38.
[35] Beddows I, et al. Cell State of Origin Impacts Development of Distinct Endometriosis-Related Ovarian Carcinoma Histotypes. *Cancer Res.* 2024; 84(1):26-38.

Acknowledging that endometriosis and ovarian cancer have some shared pathophysiology, Phung et al. (2022) published an analysis looking at the risk of developing ovarian cancer in women who self-reported a history of endometriosis in association with the presence or absence of genital application of talc.[36] Plaintiffs' expert Dr. Wolf cites to this publication claiming that it demonstrates that risk factors for ovarian cancer can interact "in a cumulative, additive, and/or synergistic fashion"[37] and claims that women in this study who had endometriosis and had exposure to talc had a higher risk of developing ovarian cancer than women without a history of endometriosis. But the confidence intervals that she cites to for women with and without endometriosis overlap and there was no statistically significant difference between the two groups. The authors themselves state, "[o]verall, we did not find any statistically significant interactions between endometriosis and the 10 ovarian cancer risk factors considered in our analysis, one of which was talc."

Tobacco

For a multitude of health reasons, use of tobacco is a poor choice. For the purposes of this review, however, there is a clear association between use of tobacco and the development of the mucinous histologic subtype of ovarian cancer.[38] Much like any environmental exposure that is found to be carcinogenic, the risk of developing ovarian cancer increases with longer durations of smoking, demonstrating an expected dose-response curve.[39]

Obesity

Not all studies have consistently demonstrated a relationship between obesity and ovarian cancer. In the studies that have demonstrated such an association, obesity seems to not only increase a woman's risk of developing ovarian cancer, but also portend a worse prognosis, with an increase in the risk of mortality.[40] A recently published umbrella review of meta-analyses confirmed previously reported data and found only a modest increase of 28% in the risk of developing ovarian cancer in women who were obese, compared with normal weight.[41] Most studies that have examined the relationship between obesity and ovarian cancer have identified a mildly increased risk in the range of 5-30%, and this risk is more commonly associated with borderline,

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[36] Phung, MT et al. 2022. Effects of risk factors for ovarian cancer in women with and without endometriosis. *Fertil. Steril.,* 118(5):960-969.

[37] Amended Rule 26 Expert Report of Judith Wolf, MD dated Nov. 15, 2023.

[38] Webb P et al. Epidemiology of epithelial ovarian cancer. *Best Practice & Research: Clinical Obstetrics & Gynecology*. 2017; 41:3-14.100

[39] Jordan SJ., et al. Does smoking increase risk of ovarian cancer? A systematic review. *Gynecologic Oncology*. 2006; 103(3):1122-9.

[40] Liu Z., et al. The association between overweight, obesity and ovarian cancer: a meta-analysis. *Japanese Journal of Clinical Oncology.* 2015; 45(12):1107-15.

[41] Chen J., et al. Body mass index and cancer risk: an umbrella review of meta-analyses of observational studies. *Nutrition & Cancer*. 2023; 75(4):1051-1064.

mucinous, endometrioid and clear cell carcinomas.[42] Ochs-Balcom et al. (2022) examined BMI and the risk of developing ovarian cancer by histotype, in African American (AA) women and White women, using subjects from the Ovarian Cancer in Women of African Ancestry (OCWAA) Consortium.[43] Similar to prior publications, the authors found an increased risk of developing ovarian cancer in women with a BMI>/30 for the non-high-grade serous histologies only, with the OR for AA women being 1.62 (1.16,2.26) and White women being 1.2 (1.02, 2.42). There was no increased risk found for the serous histology in either of the study populations.[44]

Factors Associated with a Reduction in Risk

Oral Contraceptives

There is a clear association between the use of combined oral contraceptives and a reduction in the risk of developing ovarian cancer. This holds true even for women with BRCA1 and 2 mutations.[45] Examination of the published data shows no benefit to "ever-users" (as opposed to "never-users") if the contraceptive was only used for 1-4 years.[46] Across many studies, the reduction in risk with five years or more of contiguous use has been shown to be in the range of 20-50% and continues with increasing duration of use in five-year increments. Additionally, the benefit in risk reduction is maintained for at least 30 years after cessation of the oral contraceptives, and as discussed above, is incrementally higher than that which can be attributed to the process of ovulation suppression alone.

Tubal Ligation and Hysterectomy

Women who have had a tubal ligation appear to benefit from a reduction in their risk of developing ovarian cancer by ~20-30%. The actual mechanism for this association has yet to be elucidated but seems to reduce the risk in particular of developing endometrioid and clear cell carcinomas more than invasive serous carcinomas.[47] As these two histologic subtypes are often associated with the presence of endometriosis, it may very well be that the decreased risk of ovarian cancer is the result of a reduction in the ability of ectopic endometrial tissue to pass retrograde through the interrupted fallopian tubes. This reduction in risk may last up to 30 years after the surgery is

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[42] Olsen CM., et al. Obesity and risk of ovarian cancer subtypes: evidence from the Ovarian Cancer Association Consortium. *Endocrine-Related Cancer*. 2013; 20(2):251-62.

[43] Ochs-Balcom HM, et al. Racial differences in the association of body mass index and ovarian cancer risk in the OCWAA Consortium. *Br J Cancer*. 2022 Nov;127(11):1983-1990.

[44] Ochs-Balcom HM, et al. Racial differences in the association of body mass index and ovarian cancer risk in the OCWAA Consortium. *Br J Cancer*. 2022 Nov;127(11):1983-1990.

[45] Narod S., et al. Oral contraceptives and the risk of hereditary ovarian cancer. Hereditary Ovarian Cancer Clinical Study Group. *New England Journal of Medicine*. 1998; 339(7):424-8.

[46]Collaborative Group on Epidemiological Studies of Ovarian Cancer. Ovarian cancer and oral contraceptives: collaborative reanalysis of data from 45 epidemiological studies including 23,257 women with ovarian cancer and 87,303 controls. *The Lancet*. 2008; 371(9609):303-14.

[47] Sieh W., et al. Tubal ligation and risk of ovarian cancer subtypes: a pooled analysis of case-control studies. *International Journal of Epidemiology*. 2013; 42(2):579-89.

performed. The association between having a hysterectomy and the development of ovarian cancer is less clear. Some studies have shown a reduction in risk and others have not.[48] This relationship is not as well established as the one demonstrated with tubal ligation.

Breastfeeding

Breastfeeding has been associated with a reduction in the risk of developing ovarian cancer in the range of 20-25%. Some studies have shown that the more individual children a woman breastfeeds and the longer the duration of breastfeeding, the more the risk reduction.[49] Other studies have demonstrated that for each child that is breastfed, the observed benefit to the woman seems to plateau at ~6 months of breastfeeding, which is presumably when a woman would begin to ovulate again.[50] Initially the hypothesis as to the benefit of breastfeeding was that ovulation is suppressed during the time a woman is breastfeeding; however, the actual reason that breast feeding is beneficial in reducing the risk of ovarian cancer has yet to be elucidated, as with the use of oral contraceptives. The observed reduction in risk is incrementally higher than that which can be attributed to the process of ovulation suppression alone.

Surgical Removal of the Fallopian Tubes and Ovaries

A certain percentage of high-grade serous carcinomas that were previously thought to originate in the ovary are now thought to originate in the fallopian tube. This is particularly true for women who harbor mutations in one of the genes associated with an increased risk of developing "ovarian" cancer. As such, and given that there is no effective screening for these malignancies, women considered to be at high risk for the development of cancer are often advised to have prophylactic surgical removal of these structures once they have completed their childbearing, or between the ages of 35-40 years old. This surgical procedure confers a reduction in risk of developing the disease of ~90%; a very small risk remains for primary peritoneal cancer (a malignancy that develops from the same cell of origin as ovarian cancer). Because there is presently no effective screening that can detect the development of ovarian or fallopian tube cancer in its pre-invasive or early stages *in vivo*, the risk-reducing surgery also confers a survival benefit to women at high risk for the development of these diseases.[51] In high-risk women who do not have prophylactic surgery and in whom the disease does develop,

[48] Wentzensen N., et al. Ovarian cancer risk factors by histologic subtype: an analysis from the Ovarian Cancer Cohort Consortium. *Journal of Clinical Oncology*. 2016; 34(24):2888-98.
[49] Li DP., et al. Breastfeeding and ovarian cancer risk: a systematic review and meta-analysis of 40 epidemiological studies. *Asian Pacific Journal of Cancer Prevention*. 2014; 15(12):4829-37.
[50] Jordan SJ., et al. Breastfeeding and risk of epithelial ovarian cancer. *Cancer Causes & Control*. 2010; 21(1):109-16.
[51] Domcheck SM., et al. Association of risk-reducing surgery in BRCA1 or BRCA2 mutation carriers with cancer risk and mortality 2010. *JAMA*. 304(9):967-75.

77% are diagnosed with advanced stages of cancer, which are most often incurable.[52] Importantly, women in the general population, who do not have a strong family history, or who do not carry a germline mutation in a gene that would predispose them to the development of ovarian cancer, are not counseled to proceed with risk-reducing oophorectomy, because there is clinical evidence that the ovaries provide cardiac and bone health benefits up through the natural age of menopause. ACOG is, however, presently recommending that women at low risk, who have completed their childbearing, may be offered "opportunistic salpingectomies" whereby the fallopian tubes are removed at the time of pelvic surgery being performed for some other benign indication.[53] It should be noted that this procedure is not being recommended as an independent surgical procedure for women at low risk of developing the disease. It is also noteworthy that no professional organization has ever recommended prophylactic removal of the ovaries and fallopian tubes based on a woman's history of genital application of talc.

Summary

In summary, there are several well-established risk factors that have been associated with a woman having an increased risk of developing ovarian cancer. The most influential of these are mutations in genes that can be inherited and increase the risk of developing ovarian cancer to as high as 50-60% over the course of a woman's lifetime. Genetic mutations, along with the other risk factors discussed above, are all well and generally accepted by the medical community, because of the consistency, biologic plausibility and strength of the associations in the published literature. This is evidenced by the publication of these risk factors on the respective websites of many of the most well-respected scientific organizations such as the Society of Gynecologic Oncology (SGO), the American Congress of Obstetricians and Gynecologists (ACOG), the Ovarian Cancer Research Alliance (OCRA), the American Cancer Society (ACS), the NCI and the

[52] Boyd J., et al. Clinicopathologic Features of BRCA-linked and Sporadic Ovarian Cancer. *JAMA*. 2000; 283:2060-2265.

[53] ACOG Committee Opinion No. 774 Summary: Opportunistic Salpingectomy as a Strategy for Epithelial Ovarian Cancer Prevention. *Obstetrics & Gynecology*. April 2019; 133(4): 842-43.

Centers for Disease Control (CDC).[54,55,56,57,58,59 ,60,61] Notably, none of these organizations recognizes the genital application of talc as a risk factor for the development of ovarian cancer.

Plaintiffs assert that many of these national organizations discussed above are simply "silent" on the issue of perineal application of talc and the risk of ovarian cancer. Nothing could be further from the truth.

The CDC actually recommends applying talc to the perineum after treatment of anogenital warts, as a method of abrogating any adjacent tissue damage.[62] They would be unlikely to make this recommendation if the perineal application of talc contributed to the risk of developing ovarian cancer.

The NCI issued its most recent Physician Data Query (PDQ) on ovarian cancer prevention in March 2024 and listed talc in the category of "[F]actors with inadequate evidence of an association."[63] The PDQ goes further stating that "[r]esults from case-control studies and cohort studies are inconsistent, so the data are inadequate to support an association between perineal talc exposure and an increased risk of ovarian cancer."[64] The PDQ Editorial Board's process for reviewing and analyzing peer reviewed literature to ensure that the PDQ remains current is a very detailed and meticulous process and is publicly available.[65]

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[54] Society of Gynecologic Oncology Ovarian Cancer: *Risk Factors* (last accessed May 20, 2024) https://www.sgo.org/patient-resources/ovarian-cancer/ovarian-cancer-risk-factors/

[55] ACOG: *Frequently Asked Questions Gynecologic Problems. Ovarian Cancer FAQ096*. Published April 2019; Last Updated May 2022. https://www.acog.org/womens-health/faqs/ovarian-cancer

[56] Ovarian Cancer Research Alliance: *Risk Factors* (last accessed May 20, 2024) https://ocrahope.org/patients/about-ovarian-cancer/risk-factors/

[57] National Cancer Institute, *Ovarian, Fallopian Tube and Primary Peritoneal Cancer Prevention (PDQ): Who is at Risk?* (updated March 6, 2024) https://www.cancer.gov/types/ovarian/hp/ovarian-prevention-pdq#cit/section_1.11

[58] Centers for Disease Control and Prevention. *What are the Risk Factors for Ovarian Cancer?* (August 31, 2022) https://www.cdc.gov/cancer/ovarian/basic_info/risk_factors.htm

[59] American Cancer Society. (2024). Cancer Facts & Figures 2024. *American Cancer Society.*

[60] National Cancer Institute, SEER Training Modules: *Ovarian, Fallopian Tube, and Primary Peritoneal Cancers: Risk Factors* (updated June 8, 2018) https://training.seer.cancer.gov/ovarian/intro/risk.html

[61] ACOG: Talc use and ovarian cancer. https://www.acog.org/news/news-releases/2017/09/talc-use-and-ovarian-cancer. Published September 11, 2017.

[62] Centers for Disease Control and Prevention: Sexually Transmitted Diseases Treatment Guidelines, 2015. Morbidity and Mortality Weekly Report. 2015 Jun5; 64(3):1-140).

[63] National Cancer Institute, *Ovarian, Fallopian Tube and Primary Peritoneal Cancer Prevention (PDQ): Who is at Risk?* (updated March 6, 2024) https://www.cancer.gov/types/ovarian/hp/ovarian-prevention-pdq#cit/section_1.11).

[64] National Cancer Institute, *Ovarian, Fallopian Tube and Primary Peritoneal Cancer Prevention (PDQ): Who is at Risk?* (updated March 6, 2024) https://www.cancer.gov/types/ovarian/hp/ovarian-prevention-pdq#cit/section_1.11).

[65] Manrow RE, et al. NCI's Physician Data Query (PDQ®) Cancer Information Summaries: History, Editorial Processes, Influence, and Reach. *Journal of Cancer Education*. 2014; 29(1):198-205.

In May 2021, IARC and the NCI published a joint report on future directions for ovarian cancer research. The expert panel consisted of members of IARC and the NCI as well as several internationally respected ovarian cancer researchers from major comprehensive cancer centers around the globe. Nowhere within this report is talc listed as a risk factor or causative agent for the development of ovarian cancer. Additionally, despite a clear call for high priority research to focus on risk factors related to premenopausal exposures, concentrating on known and putative risk factors, the perineal application of talc is not even mentioned in this report.[66]

The Ovarian Cancer Research Alliance ("OCRA") recently updated the "Get the Facts" section of their website, specifically addressing the purported relationship between talcum powder and ovarian cancer. They posted "Ovarian Cancer Research Alliance provides information based on medical research and best practices. **Research regarding a connection between the use of talcum powder and increased ovarian cancer risk is inconclusive."** (Bold is from original post). President and CEO of the OCRA, Audra Moran, stated "In highly publicized cases, we must be careful as a women's health organization to let science guide our reactions. The fact remains that the science is inconclusive about increased risk of ovarian cancer to women using talcum powder."[67]

The American Cancer Society (ACS) concurs. In their most recent publication, "Cancer Facts & Figures 2024" they state "[t]he weight of the evidence does not support an association between ovarian cancer and genital exposure to talc-based powder."[68] Plaintiffs' expert Dr. Wolf misrepresents the ACS's position on the risk of developing ovarian cancer and the genital application of talc when she claims in deposition testimony that "[t]he American Cancer Society lists [talc use] as a possible cause and recommends further investigation."[69] This is simply not true, as referenced above.

In 2017, ACOG issued a letter to its membership stating that there is "no medical consensus that talcum powder causes ovarian cancer."[70] And as recently as May 2023, at ACOG's Annual Clinical and Scientific Meeting, the executive summary of the ovarian cancer evidence review conference was presented and the authors concluded that "[t]he studies regarding the use of talcum powder and the risk of ovarian cancer are heterogeneous."[71] They then go on to cite to NCCN guidelines and report, "that

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[66] Virani S., et al. Joint IARC/NCI International Cancer Seminar Series Report: expert consensus on future directions for ovarian carcinoma research. *Carcinogenesis*. 2021; 42(6):785-93.
[67] Ovarian Cancer Research Alliance (OCRA): Get the Facts (last accessed May 20, 2024) https://ocrahope.org/get-the-facts/faq/talcum-powder-and-ovarian-cancer/
[68] American Cancer Society. (2024). Cancer Facts & Figures 2024. *American Cancer Society.*
[69] January 10, 2024 Deposition Transcript of Judith Wolf, MD, p. 60:2-5.
[70] American College of College of Obstetrics and Gynecologists: Talc use and ovarian cancer. https://www.acog.org/news/news-releases/2017/09/talc-use-and-ovarian-cancer. Published September 11, 2017.
[71] Burke, W., et al. Executive Summary of the Ovarian Cancer Evidence Review Conference with Appendices. *Obstet Gynecol.* 2023; 142:179-95.

environmental factors have not been conclusively associated with the development of ovarian cancer." This executive summary was convened by ACOG to develop educational materials for clinicians on gynecologic cancers and consisted of a panel of experts in evidence review from the Society for Academic Specialists in General Obstetrics and Gynecology and content experts from the SGO and was funded by a grant from the CDC. The review also contained a section on substantive knowledge gaps to provide guidance for future research and notably, there was no call for additional research on talc as a risk factor for the development of ovarian cancer.

The NCCN reiterated its position that talc is not associated with an increased risk of developing ovarian cancer in its January 2024 Clinical Practice Guidelines in Oncology addressing ovarian, fallopian tube and primary peritoneal cancers where it stated, "[e]nvironmetal factors have been investigated, such as talc, but so far they have not conclusively been associated with the development of this neoplasm."[72]

Clearly, the consensus of the science is that talc is not a risk factor for the development of ovarian cancer, and it certainly is not a causative agent.

Talc and the Risk of Ovarian Cancer – Overview

The proposed association between use of talc in the genital area and an increased risk of ovarian cancer was first reported ~40 years ago, yet this assertion remains unsubstantiated with no credible science and a lack of biologic plausibility as to a mechanism of carcinogenicity. Similar hypotheses have been published throughout the years regarding environmental exposures (e.g. eating processed meat, chronic physical inactivity or watching television for >5 hours per day), as all increasing the risk of ovarian cancer. For each of these hypotheses, there is epidemiological literature that has demonstrated statistically significant associations between these factors and the occurrence of ovarian cancer all with ORs in the range 1.34-2.16.[73,74,75,76] But an association (especially a modest one) is not determinative of a causal relationship, and talc is no more causal of ovarian cancer than watching television,

Despite many years of research on this topic, the scientific evidence does not support a causal role in the development of ovarian cancer with the application of talc to the perineal region. First, the epidemiologic literature on this topic is inconsistent. The

[72] National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology. Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer. Version 1.2024 at p. 70.
[73] Cannioto R., et al. Chronic recreational physical inactivity and epithelial ovarian cancer risk: evidence from the Ovarian Cancer Association Consortium. *Cancer Epidemiology and Prevention Biomarkers*. 2016; 25(7):1114-24.
[74] Rosato V., et al. Processed meat and selected hormone-related cancers. *Nutrition*. 2018; 49:17-23.
[75] Ukawa S., et al. Association between average daily television viewing time and the incidence of ovarian cancer: findings from the Japan Collaborative Cohort Study. *Cancer Causes & Control*. 2018; 29(2):213-9.

majority of the published studies consists of small retrospective case-control studies with inherent selection and recall biases. Many of these studies have internal discrepancies and contradict each other, and none of them is able to demonstrate a consistent dose-response curve, nor a threshold-dose. Three independent cohort studies have been published on this subject, and these studies have enrolled large numbers of women, who were followed prospectively, thus removing selection and recall biases, making the data and outcomes more credible.[77,78,79,80] None of the cohort studies demonstrates a statistically significant association between talc and ovarian cancer. In 2020, O'Brien et al. published a pooled analysis of the above mentioned 3 independent cohort studies and included additional subjects from the Nurses' Health Study II, creating a cohort of more than 250,000 women and found no statistically significant increase in the risk of developing ovarian cancer with perineal talc use.[81]

Based mainly on data pulled from the case-control studies, several meta-analyses and one pooled analysis have also been published.[82,83,84,85] Some authors have proposed the use of pooled analyses and meta-analyses to group the case-control studies together to give more power to the association, but this logic does not always result in stronger science, as these larger studies are subject to the same design errors and biases of the original studies from which they were combined. By and large, the meta-analyses all show the same modest increase in odds ratio in the range of 1.24-1.4. The primary reason for the consistency across the meta-analyses is very likely the fact that they all used many of the same case-control studies in each of the analyses. Simply put, they re-churned overlapping data sets.

A key component of the hypothesis that perineal application of talc can increase the risk of ovarian cancer is the proposal that the talc can migrate from the perineum to the ovaries. The female genital tract, however, is not an open system. Substances do not freely traverse from the vulva to the ovaries. In fact, there is not a single study demonstrating such migration from the external perineum up through the reproductive

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[77] Gates MA., et al. Risk factors for epithelial ovarian cancer by histologic subtype. *American Journal of Epidemiology*. 2010; 171:45-53.
[78] Gertig DM., et al. Prospective study of talc use and ovarian cancer. *Journal of the National Cancer Institute.* 2000; 92:249-52.
[79] Houghton SC., et al. Perineal powder use and risk of ovarian cancer. *Journal of the National Cancer Institute.* 2014; 106(9):208.
[80] Gonzalez N., et al. Douching, talc use, and risk of ovarian cancer. *Epidemiology.* 2016; 27(6):797-802.
[81] O'Brien, KM, et al. Association of powder use in the genital area with risk of ovarian cancer. *JAMA* 2020; 323(1), 49-59.
[82] Terry KL., et al. Genital powder use and risk of ovarian cancer: A pooled analysis of 8,525 cases and 9,859 controls. *Cancer Prevention Research*. 2013; 6(8):811-21.
[83] Berge W., et al. Genital use of talc and risk of ovarian cancer: a meta-analysis. *European Journal of Cancer Prevention.* 2018; 27(3):248-57.
[84] Penninkilampi R., et al. Perineal talc use and ovarian cancer: A systematic review and meta-Analysis. *Epidemiology.* 2018; 29(1):41-9.
[85] Taher M., et al., Critical Review of the Association between Perineal Use of Talc Powder and Risk of Ovarian Cancer. *Reproductive Toxicology*. 2019; 90:88-101.

tract to the ovaries. Nor is there a single publication that identifies inflammation anywhere in a woman's reproductive tract resulting from external talc application to the perineal area. This last fact is particularly germane, as plaintiffs' experts have proposed that the mechanism by which talc reportedly induces ovarian cancer is through the induction of a chronic inflammatory response. This too is pure conjecture, as there is no direct evidence that chronic inflammation causes ovarian cancer, and chronic inflammatory states such as IUD use and pelvic inflammatory disease have not consistently been shown to be associated with an increased risk of developing ovarian cancer. Additionally, the literature on the use of anti-inflammatory agents (aspirin and NSAIDs) has not consistently been shown to decrease the risk of developing ovarian cancer, as it has in malignancies that are known to arise from induction of a chronic inflammatory state (*e.g.,* colon cancer). Recently, the ACS has suggested that frequent aspirin use may be associated with a reduced risk of developing ovarian cancer, although they also caution that this can have serious adverse health effects and should only be done in consultation with a health care provider.[86] Citing to several of the studies with conflicting results, the NCI PDQ categorizes aspirin and NSAIDs as "factors with inadequate evidence of an association risk of ovarian cancer."[87] Given the additional health risks associated with frequent aspirin use and the conflicting data found in recent publications, recommendations for regular aspirin use as a risk reduction strategy have not been adopted into clinical practice the way that recommendations for OCP use have, where the reduction in risk approaches 50%.

The following section of this report provides a thorough discussion of the epidemiologic literature that has been published on this subject and also reviews plaintiffs' theories of talc migration and inflammation as the underlying mechanism by which talc causes an increase in the risk of developing ovarian cancer. Based upon my expertise, a thorough assessment of the literature, and weighing of the criteria initially proposed by Sir Bradford Hill[88] to determine if causation can be deduced from an observed association, it is my opinion there is no support for the perineal application of talc as a cause of ovarian cancer. Following is an analysis of the factors that I deem most important in making this determination, including the fact that there is no strength of association, there is a lack of consistency in the literature, there is no evidence of a dose response, and there is a lack of biologic plausibility in terms of migration, inflammation, and malignant transformation. This analysis is supported in the peer-reviewed published literature where the case for an association between talc exposure and the risk of ovarian cancer has been subjected to comprehensive reviews and found to fail the Hill

[86] American Cancer Society. (2024). Cancer Facts & Figures 2024. *American Cancer Society* at p. 23.
[87] National Cancer Institute, *Ovarian, Fallopian Tube and Primary Peritoneal Cancer Prevention (PDQ): Who is at Risk?* (updated March 6, 2024) https://www.cancer.gov/types/ovarian/hp/ovarian-prevention-pdq#cit/section_1.11
[88] Hill, A.B. (1965). The Environment and Disease: Association or Causation? *Proceedings of the Royal Society of Medicine*, 58(5), 295-300.

criteria.[89,90] Moreover, since Dr. Hill initially published his paper almost 60 years, the scientific world has advanced significantly in the fields of cancer and molecular biology, and those advances should be considered in conjunction with the epidemiologic data when defining causal relationships in diseases as complex as cancer.

Epidemiologic Literature

Case-Control Studies

Various searches of the peer-reviewed literature reveal approximately 32 case-control studies that have been published on the association between the perineal use of talc and the development of ovarian cancer. Some of the studies, however, have either republished previously published data sets, adding new "findings" and calling it a new study,[91,92] or they have subsumed the data from an earlier publication and then added additional subjects for the later publication, thereby calling it an original study.[93,94,95,96,97,98] When the four case-control studies that had their data subsumed into later publications are eliminated from the analysis, this leaves 27 original case-control studies that examine the potential association between perineal talc use and ovarian cancer. Of these 27 published studies, only 13 found a statistically significant increased risk of developing ovarian cancer with the ever-use of talc in the perineal area as compared to never users. This means that 52%, or more than half of the original published case-control literature did not find a statistically significant association between talc and ovarian cancer (Table 1). None of the studies found an odds ratio of >2 when looking at never/ever perineal use of talc and ovarian cancer. One study that looked at differential risks in African-American (AA) women as compared with Caucasian (Cau) women found a statistically significant increased risk only in the Caucasian

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[89] Dragani, Ta., Difficulties in establishing a causal link between chemical exposures and cancer cannot be overcome by court assessments. *Human & Experimental Toxicology* 2020; 39(8):1095-1107.

[90] National Cancer Institute, *Ovarian, Fallopian Tube and Primary Peritoneal Cancer Prevention (PDQ): Who is at Risk?* (updated March 6, 2024) https://www.cancer.gov/types/ovarian/hp/ovarian-prevention-pdq#cit/section_1.11.

[91] Green A., et al. Tubal sterilisation, hysterectomy and decreased risk of ovarian cancer. *International Journal of Cancer*. 1997; 71(6):948-51.

[92] Purdie D., et al. Reproductive and other factors and risk of epithelial ovarian cancer: An Australian case-control study. Survey of Women's Health Study Group. *International Journal of Cancer*. 1995; 62:678-84.

[93] Cramer DW., et al. Genital talc exposure and risk of ovarian cancer. *International Journal of Cancer*. 1999; 81(3):351-6.

[94] Cramer DW., et al. The association between talc use and ovarian cancer: A retrospective case-control study in two US states. *Epidemiology*. 2016; 27(3):334-46.

[95] Gabriel I., et al. Douching, Talc Use, and Risk of Ovarian Cancer and Conditions Related to Genital Tract Inflammation. *Cancer Epidemiol. Biomarkers Prev.* 2019; 28:1835-44.

[96] Pike MC., et al. Hormonal factors and the risk of invasive ovarian cancer: a population-based case-control study. *Fertility and Sterility*. 2004; 82(1):186-95.

[97] Wu AH., et al. Markers of inflammation and risk of ovarian cancer in Los Angeles County. *International Journal of Cancer*. 2009; 124:1409-15.

[98] Wu AH., et al. African Americans and Hispanics remain at lower risk of ovarian cancer than non-Hispanic Whites after considering non-genetic risk factors and oophorectomy rates. *Cancer Epidemiology, Biomarkers & Prevention*. 2015 24(7):1094-100.

women.[99] This is a most interesting finding as both the African American cases and controls were found to have a higher prevalence of ever use, more frequent use and long-term use of genital powder than Caucasian cases and controls. This study highlights one of the paradoxical findings that is evident in the case-control literature on the genital application of talc and the risk of ovarian cancer – how is it that the population of women (African American) that is using more talc for longer periods of time and more frequent applications has a lower, non-statistically significant risk of developing the disease if the talc is causal? Not surprisingly, this study by Davis et al., also reported that the authors found no evidence of a dose response relationship even though they collected data on both frequency and duration of use.

[99] Davis CP., et al. Genital powder use and risk of epithelial ovarian cancer in the Ovarian Cancer in Women 2 of African Ancestry Consortium. *Cancer Epidemiology and Prevention Biomarkers*. 2021; 30(9)1660-1668.

TABLE 1: CASE CONTROL STUDIES:

	OR (CI) ever/never genital use	SS or NS
Davis 2021[100]	**1.22 (0.97,1.53) (AA)**	**NS**
	1.36 (1.19,1.57) (Cau)	SS
Schildkraut 2016 [101]	1.44 (1.11,1.86)	SS
Cramer 2016 [102]	1.33 (1.16,1.52)	SS
Wu 2015 [103]	1.46 (1.27,1.69)	SS
Kurta 2012 [104]	1.40 (1.16,1.69)	SS
Lo-Ciganic 2012* [105]	1.34 (1.07,1.67)	SS
Rosenblatt 2011 [106]	**1.27 (0.97,1.66)**	**NS**
Moorman 2009 [107]	**1.04 (0.82,1.33) (Cau)**	**NS**
	1.19 (0.68,2.09) (AA)	**NS**
Merritt 2008 [108]	1.17 (1.01,1.36)	SS
Gates 2008 [109]	1.36 (1.14,1.63)	SS
Goodman 2008* [110]	**0.99 (0.7,1.41)**	**NS**
Mills 2004 [111]	1.37 (1.02,1.85)	SS
Ness 2000 [112]	1.5 (1.1,2.0)	SS

[100] Davis CP., et al. Genital powder use and risk of epithelial ovarian cancer in the Ovarian Cancer in Women 2 of African Ancestry Consortium. *Cancer Epidemiology and Prevention Biomarkers*. 2021; 30(9)1660-1668.
[101] Schildkraut JM., et al. Association between body powder use and ovarian cancer: the African American Cancer Epidemiology Study (AACES). *Cancer Epidemiology and Prevention Biomarkers*. 2016; cebp-1281.
[102] Cramer DW., et al. The association between talc use and ovarian cancer: A retrospective case-control study in two US states. *Epidemiology*. 2016; 27(3):334-46.
[103] Wu AH., et al. African Americans and Hispanics remain at lower risk of ovarian cancer than non-Hispanic Whites after considering non-genetic risk factors and oophorectomy rates. *Cancer Epidemiology, Biomarkers & Prevention*. 2015 24(7):1094-100.
[104] Kurta ML., et al. Use of fertility drugs and risk of ovarian cancer: Results from a US-based case-control study. *Cancer Epidemiology and Prevention Biomarkers*. 2012; 21(8), 1282-92.
[105] Lo-Ciganic WH., et al. Aspirin, non-aspirin nonsteroidal anti-inflammatory drugs, or acetaminophen and risk of ovarian cancer. *Epidemiology*. 2012; 23(2):311-9.
[106] Rosenblatt KA., et al. Genital powder exposure and the risk of epithelial ovarian cancer. *Cancer Causes & Control*. 2011; 22(5):737-42.
[107] Moorman PG., et al. Ovarian cancer risk factors in African American and White women. *American Journal of Epidemiology*. 2009; 170(5):598-606.
[108] Merritt MA., et al. Talcum powder, chronic pelvic inflammation and NSAIDs in relation to risk of epithelial ovarian cancer. *International Journal of Cancer*. 2008; 122(1):170-6.
[109] Gates MA., et al. Talc use, variants of the GSTM1, GSTT1, and NAT2 genes, and risk of epithelial ovarian cancer. *Cancer Epidemiology, Biomarkers & Prevention*. 2008; 17(9):2436-44.
[110] Goodman MT., et al. Association of two common single-nucleotide polymorphisms in the CYP19A1 locus and ovarian cancer risk. *Endocrine-related Cancer*. 2008; 15(4):1055-60.
[111] Mills PK., et al. Perineal talc exposure and epithelial ovarian cancer risk in the Central Valley of California. *International Journal of Cancer*. 2004; 112:458-64.
[112] Ness RB., et al. Factors related to inflammation of the ovarian epithelium and risk of ovarian cancer. *Epidemiology*. 2000; 11:111-7.

Wong 1999 [113]	**1.0 (0.8,1.3)**	**NS**
Godard 1998 [114]	**2.49 (0.94,6.58)**	**NS**
Green 1997[115]	1.30 (1.10,1.60)	SS
Cook 1997 [116]	**1.6 (0.9,2.80)**	**NS**
Chang 1997 [117]	1.42 (1.08,1.86)	SS
Tzonou 1993 [118]	**1.05 (0.28,3.98)**	**NS**
Harlow 1992 [119]	**1.5 (1.0,2.1)**	**NS**
Rosenblatt 1992 [120]	**1.70 (0.70,3.90)**	**NS**
Chen 1992 [121]	**3.90 (0.90,10.63)**	**NS**
Booth 1989 [122]	**1.30 (0.8,1.90)**	**NS**
Harlow 1989 [123]	**1.10 (0.70,2.10)**	**NS**
Whittemore 1988 [124]	**1.45 (0.81,2.60)**	**NS**
Hartge 1983 [125]	**2.5 (0.7,10.0)**	**NS**
Cramer 1982 [126]	1.92 (1.27,2.89)	SS

OR = odds ratio; CI = confidence interval; SS = statistically significant (listed as black); NS = not statistically significant (listed as green). Table excludes studies whose data was subsumed into another publication.

[113] Wong C., et al. Perineal talc exposure and subsequent epithelial ovarian cancer: A case-control study. *Obstetrics & Gynecology*. 1999; 93:372-6.
[114] Godard B., et al. Risk factors for familial and sporadic ovarian cancer among French Canadians: a case-control study. *American Journal of Obstetrics and Gynecology*. 1998; 179(2):403-10.
[115] Green A., et al. Tubal sterilisation, hysterectomy and decreased risk of ovarian cancer. *International Journal of Cancer*. 1997; 71(6):948-51.

[116] Cook LA., et al. Perineal powder exposure and the risk of ovarian cancer. *American Journal of Epidemiology*. 1997; 145:459-65.
[117] Chang S., et al. Perineal talc exposure and risk of ovarian carcinoma. *Cancer*. 1997; 79:2396-401.
[118] Tzonou A., et al. Hair dyes, analgesics, tranquilizers and perineal talc application as risk factors for ovarian cancer. *International Journal of Cancer*. 1993; 55:408-10.
[119] Harlow BL., et al. Perineal exposure to talc and ovarian cancer risk. *Obstetrics & Gynecology*. 1992; 80:19-26.
[120] Rosenblatt KA., et al. Mineral fiber exposure and the development of ovarian cancer. *Gynecologic Oncology*. 1992; 45:20-5.
[121] Chen Y., et al. Risk factors for epithelial ovarian cancer in Beijing, China. *International Journal of Epidemiology*. 1992; 21(1): 23-9.
[122] Booth M., et al. Risk factors for ovarian cancer: a case-control study. *British Journal of Cancer*. 1989; 60:592-8.
[123] Harlow BL et al., A case-control study of borderline ovarian tumors: the influence of perineal exposure to talc. *American Journal of Epidemiology*. 1989; 130(2):390-4.
[124] Whittemore AS., et al. Personal and environmental characteristics related to epithelial ovarian cancer. II. Exposures to talcum powder, tobacco, alcohol, and coffee. *American Journal of Epidemiology*. 1988; 128:1228-40.
[125] Hartge P., et al. Talc and ovarian cancer. *JAMA*. 1983; 250:1844.
[126] Cramer DW., et al. Ovarian cancer and talc. A case-control study. *Cancer*. 1982; 50(2):372-6.

In the studies that did find a statistically significant association, the typical odds ratio was in the range of 1.3-1.5, which is at most, a modest increase and could still be attributable to random chance, confounding or bias, as the strength of the association is weak. At times plaintiffs have asserted that statistical significance is not important in evaluating these studies and the association between perineal talc use and the development of ovarian cancer. They have proposed that since most of the ORs are all greater than 1, that is all we should look at and accept the trend regardless of statistical significance. But abandoning sound principles of statistical analysis is not the way credible science is conducted nor evaluated.

Several of the case-control studies that report positive associations between talc and ovarian cancer suffer from internal inconsistencies. Wu (2009) clearly has methodological problems, as in the analysis the authors report that family history was not significantly associated with the development of ovarian cancer with an OR of 1.76 (CI 0.89,3.47).[127] In the medical and scientific communities, one of the most well accepted and established facts about ovarian cancer is that having a family member with either ovarian or breast cancer raises an individual woman's risk of developing ovarian cancer at least three times higher than the background population risk.[128,129] But the Wu (2009) study – which examined this relationship as an "internal control" – failed to demonstrate a statistically significant association between a family history of breast or ovarian cancer and the development of ovarian cancer.[130] This failure of the study's own "internal control" to replicate the well-established association between family history and the development of ovarian cancer undermines the credibility of all of the findings in Wu (2009).

Cramer (2016) reports an OR of 1.33 (CI 1.16,1.52) for ever vs. never use of talc and the development of ovarian cancer.[131] As discussed more fully below, the authors of this study falsely assert that they demonstrate a dose-response curve with their data, incorrectly stating that subjects were found to have an increased risk the more frequently they applied talc perineally. They also report a positive finding for years used; however, the reported odds ratios are actually flat, with the OR for < 8 years of exposure being essentially the same as > 35 years of exposure (1.31 vs. 1.33). Additionally, when they calculated total lifetime applications (based on years of use and frequency of application), their data was sinusoidal, fluctuating up and down with 1-5

[127] Wu AH., et al. Markers of inflammation and risk of ovarian cancer in Los Angeles County. *International Journal of Cancer*. 2009; 124:1409-15.
[128] Kazerouni N., et al. Family history of breast cancer as a risk factor for ovarian cancer in a prospective study. Cancer: *Interdisciplinary International Journal of the American Cancer Society.* 2006; 107(5):1075-83.
[129] Sutcliffe S., et al. Familial Ovarian Cancer Study Group. Ovarian and breast cancer risks to women in families with two or more cases of ovarian cancer. *International Journal of Cancer*. 2000; 87(1):110-7.
[130] Wu AH., et al. Markers of inflammation and risk of ovarian cancer in Los Angeles County. *International Journal of Cancer*. 2009; 124:1409-15.
[131] Cramer DW., et al. The association between talc use and ovarian cancer: A retrospective case-control study in two US states. *Epidemiology*. 2016; 27(3):334-46.

years of daily use being significant but > 5-20 years of daily use being not significant and then > 20 years of daily use being significant. (See Table 1 from Cramer (2016) discussed below.) The internal inconsistencies of reporting that 5-20 years of use does not increase the risk of ovarian cancer, but 8-19 years of use does result in an increased risk, calls into question the validity of the entire study. As responsible researchers, the authors cannot and should not cherry pick the findings that support their hypotheses, while minimizing the results that do not support their suppositions.

Cramer (1999) suffers from the same pitfall. Despite reporting an OR of 1.6 (CI 1.18,2.15) for ever vs. never perineal use of talc, the authors also found that the more applications of talc per month, the risk of ovarian cancer becomes less significant, with <30 applications per month doubling a woman's risk and then with 30-39 applications per month decreasing to a non-statistically significant OR of 1.17 and then 40+ applications per month increasing the OR slightly to 1.57 and again being a not statistically significant finding.[132] This back and forth with statistically significant findings at one dose and non-statistically significant findings with lower ORs at higher doses contradicts what we know is the definition of a dose response. The risk should continue to increase (or at a minimum plateau) with more exposure, not become less significant or be sinusoidal, as in Cramer (1999, 2016).[133,134]

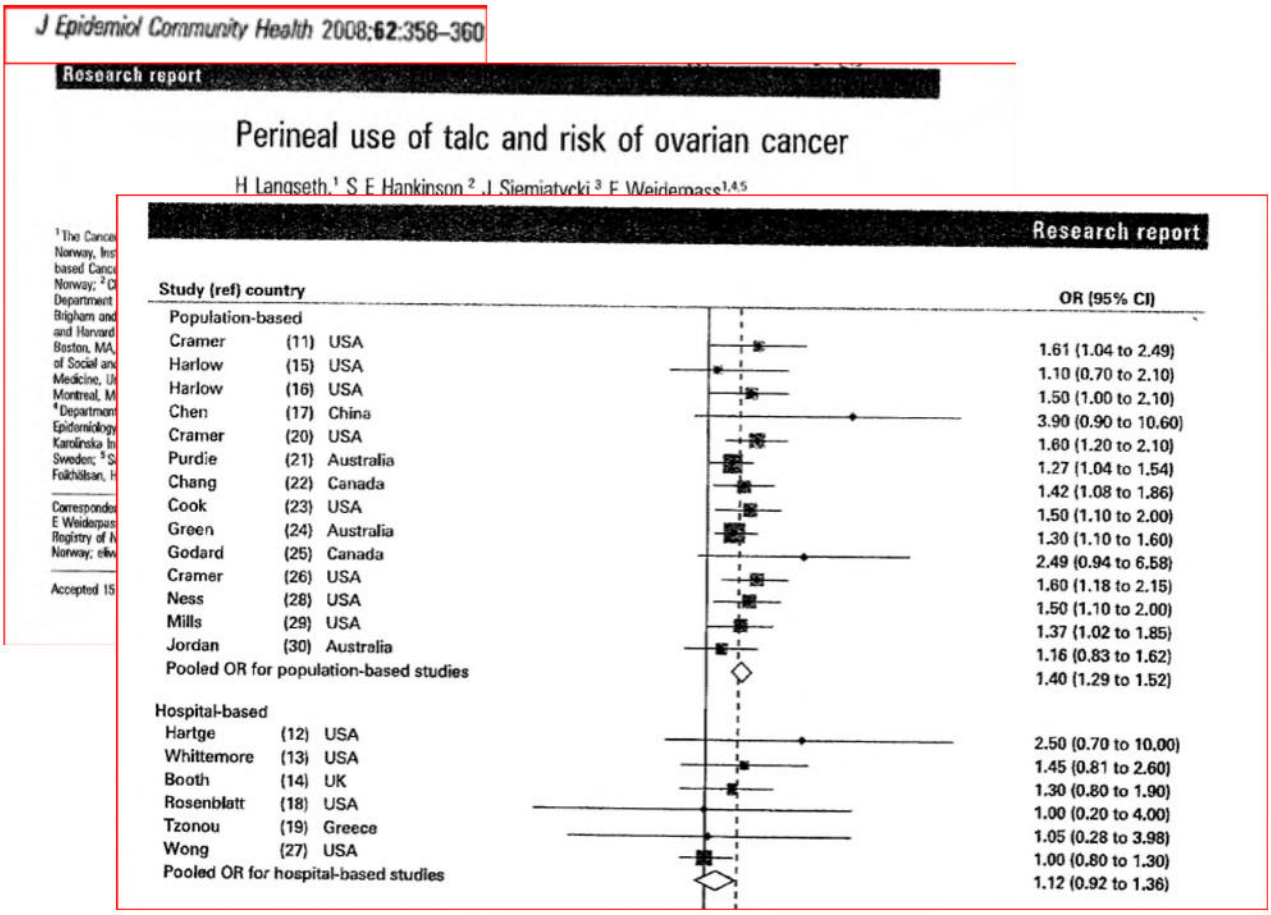
As stated above, one of the most glaring deficiencies in the case-control literature has been the lack of a consistent dose-response curve, or biologic gradient. Like any other environmental exposure, if talc is a causal agent in the development of ovarian cancer, then there should be a clear dose-response curve with increasing exposure to talc leading to an increased risk of developing ovarian cancer. Langseth (2008) published a meta-analysis of the available literature as of that date, which consisted of 20 case-control studies and one cohort study.[135] The authors noted specifically that 10 of the case-control studies reported statistically significant increased risks and the remaining 10 studies reported non-statistically significant risks, with several of the studies unable to establish a dose-response curve with exposure to talc in terms of either frequency of

[132] Cramer DW., et al. Genital talc exposure and risk of ovarian cancer. *International Journal of Cancer*. 1999; 81(3):351-6.
[133] Cramer DW., et al. Genital talc exposure and risk of ovarian cancer. *International Journal of Cancer*. 1999; 81(3):351-6.
[134] Cramer DW., et al. The association between talc use and ovarian cancer: A retrospective case-control study in two US states. *Epidemiology*. 2016; 27(3):334-46.
[135] Langseth H., et al. Perineal use of talc and risk of ovarian cancer. *Journal of Epidemiology and Community Health*. 2008; 62(4):358-60.

applications or length of use in years.[136,137,138,139,140,141] They also reported that "the main epidemiological evidence against the association [between talc and ovarian cancer] is the absence of clear exposure-response associations in most studies." Additional, more recent studies have also failed to demonstrate a clear dose-response curve, including Davis (2021), Penninkilampi (2018), Schildkraut (2016), Terry (2013) and Wu (2009).[142,143,144,145,146]

Another interesting observation from the Langseth paper was that while 10 of the 14 case-control studies that were conducted as population-based studies reported a statistically significant increase in the OR for the development of ovarian cancer with talc use in the perineal area (see table below), none of the hospital-based studies reported statistically significant results, both individually (6/6), and collectively as a meta-analysis (OR 1.12; CI 0.92,1.36).[147]

[136] Booth M., et al. Risk factors for ovarian cancer: a case-control study. *British Journal of Cancer*. 1989; 60:592-8.
[137] Chang S., et al. Perineal talc exposure and risk of ovarian carcinoma. *Cancer*. 1997; 79:2396-401.
[138] Cook LA., et al. Perineal powder exposure and the risk of ovarian cancer. *American Journal of Epidemiology*. 1997; 145:459-65.
[139] Cramer DW., et al. Genital talc exposure and risk of ovarian cancer. *International Journal of Cancer*. 1999; 81(3):351-6.
[140] Ness RB., et al. Factors related to inflammation of the ovarian epithelium and risk of ovarian cancer. *Epidemiology*. 2000; 11:111-7.
[141] Whittemore AS., et al. Personal and environmental characteristics related to epithelial ovarian cancer. II. Exposures to talcum powder, tobacco, alcohol, and coffee. *American Journal of Epidemiology*. 1988; 128:1228-40.
[142] Davis CP., et al. Genital powder use and risk of epithelial ovarian cancer in the Ovarian Cancer in Women 2 of African Ancestry Consortium. *Cancer Epidemiology and Prevention Biomarkers*. 2021; 30(9)1660-1668.
[143] Penninkilampi R., et al. Perineal talc use and ovarian cancer: A systematic review and meta-Analysis. *Epidemiology*. 2018; 29(1):41-9.
[144] Schildkraut JM., et al. Association between body powder use and ovarian cancer: the African American Cancer Epidemiology Study (AACES). *Cancer Epidemiology and Prevention Biomarkers*. 2016; cebp-1281.
[145] Terry KL., et al. Genital powder use and risk of ovarian cancer: A pooled analysis of 8,525 cases and 9,859 controls. *Cancer Prevention Research*. 2013; 6(8):811-21.
[146] Wu AH., et al. Markers of inflammation and risk of ovarian cancer in Los Angeles County. *International Journal of Cancer*. 2009; 124:1409-15.
[147] Langseth H., et al. Perineal use of talc and risk of ovarian cancer. *Journal of Epidemiology and Community Health*. 2008; 62(4):358-60.



J Epidemiol Community Health 2008;62:358–360

Research report

Perineal use of talc and risk of ovarian cancer

H Langseth,[1] S E Hankinson,[2] J Siemiatycki,[3] E Weiderpass[1,4,5]

Research report

Study (ref) country			OR (95% CI)
Population-based			
Cramer	(11)	USA	1.61 (1.04 to 2.49)
Harlow	(15)	USA	1.10 (0.70 to 2.10)
Harlow	(16)	USA	1.50 (1.00 to 2.10)
Chen	(17)	China	3.90 (0.90 to 10.60)
Cramer	(20)	USA	1.60 (1.20 to 2.10)
Purdie	(21)	Australia	1.27 (1.04 to 1.54)
Chang	(22)	Canada	1.42 (1.08 to 1.86)
Cook	(23)	USA	1.50 (1.10 to 2.00)
Green	(24)	Australia	1.30 (1.10 to 1.60)
Godard	(25)	Canada	2.49 (0.94 to 6.58)
Cramer	(26)	USA	1.60 (1.18 to 2.15)
Ness	(28)	USA	1.50 (1.10 to 2.00)
Mills	(29)	USA	1.37 (1.02 to 1.85)
Jordan	(30)	Australia	1.16 (0.83 to 1.62)
Pooled OR for population-based studies			1.40 (1.29 to 1.52)
Hospital-based			
Hartge	(12)	USA	2.50 (0.70 to 10.00)
Whittemore	(13)	USA	1.45 (0.81 to 2.60)
Booth	(14)	UK	1.30 (0.80 to 1.90)
Rosenblatt	(18)	USA	1.00 (0.20 to 4.00)
Tzonou	(19)	Greece	1.05 (0.28 to 3.98)
Wong	(27)	USA	1.00 (0.80 to 1.30)
Pooled OR for hospital-based studies			1.12 (0.92 to 1.36)

This fact that none of the studies that had hospital-based controls found a statistically significant association between perineal application of talc and developing ovarian cancer has been interpreted as overt evidence of the recall bias that is inherent not just in the case-control studies on talc and ovarian cancer, but in all case-control studies. People who have had more time to perseverate and consider every detail and aspect of their lives that may have factored into how they developed a certain disease state, in this case, ovarian cancer, are much more likely to report, if not over-report, a positive association with a certain exposure as they search for answers as to what may have caused them to be diagnosed with this condition. Use of talcum powder is self-reported data and is subject to recall bias, especially for factors such as the frequency of use per month and years of use. Additionally, the data can be influenced by the investigator in terms of the manner in which a question is asked or by the explanation of the intent of the study. This bias is inherently much stronger for case-control studies over any other study design, as the women selected as cases have necessarily been diagnosed with ovarian cancer in order to be selected for the study.

Finally, as we consider additional biases that impact the scientific literature on the relationship between talc and ovarian cancer, we must address the times we live in and social media and the publicity of talc litigation. Schildkraut (2016) analyzed their results

by subjects interviewed before and after 2014 (when the media began heavily reporting about talc litigation).[148] The authors found that in women with ovarian cancer who were interviewed in 2014 or later, any reported use of talc was 12% higher than in women interviewed prior to 2014. This change in reporting rate resulted in an OR that was not statistically significant at 1.19 (CI 0.87,1.63) prior to 2014, rising to a statistically significant result of 2.91 (CI 1.70, 4.97) after 2014. Additionally, a test for the influence of year of reporting was found to be statistically significant and the authors offer that misclassification exists in case-control studies such as this, especially due to heightened awareness and publicity surrounding the lawsuits. Recognizing the influence and potential for biases introduced into their study by the talc litigation, the authors specifically analyzed their data in terms of prevalence of use and year of interview, pre- and post-2014. Recall bias and reporting bias were in fact documented by these authors, resulting in the inflation of the odds ratio from a non-statistically significant value to a statistically significant one, almost 2.5 times higher.[149] This is an especially stark finding that validates the suggestions of authors well prior to 2014 that recall bias could be driving the results of case-control studies of talc and ovarian cancer.

Further evidence that ovarian cancer survivors may be more susceptible to recall bias when self-reporting genital talc use is found in a 2023 publication by O'Brien et al. that sought to evaluate the reliability of self-reported exposure by querying women on genital talc use at two different time points.[150] The authors performed a follow-up study to the Sister Study[151] which initially queried women at enrollment (2003-2009) regarding their use of talc and douching products at ages 10-13 and during the twelve consecutive months prior to study enrollment. On a follow-up questionnaire (2017-2019), these same women were again asked to report on their use of these products between the ages of 10-13 and over the course of their lifetimes. The authors reported that in women with intervening ovarian cancer diagnoses, 28% initially self-reported genital talc use, and then the percentage rose to 33% self-reporting genital talc use on the follow-up questionnaire, after these women had been diagnosed with ovarian cancer. The authors also point out that this was the *only* subgroup for which the proportion of users increased between enrollment and follow-up, and correctly propose that this could reflect recall bias.

Cohort Studies

Three independent prospective cohort studies and one pooled analysis (with additional study subjects previously not included in the 3 prior analyses), have been published on the potential relationship between talc and the development of ovarian cancer. One of

[148] Schildkraut JM., et al. Association between body powder use and ovarian cancer: the African American Cancer Epidemiology Study (AACES). *Cancer Epidemiology and Prevention Biomarkers. 2016*; cebp-1281.
[149] Schildkraut JM., et al. Association between body powder use and ovarian cancer: the African American Cancer Epidemiology Study (AACES). *Cancer Epidemiology and Prevention Biomarkers*. 2016; cebp-1281.
[150] O'Brien K., et al. Douching and genital talc use: patterns of use and reliability of self-reported exposure. *Epidemiology.* 2023; 34(3): 376-384.
[151] Gonzalez N., et al. Douching, talc use, and risk of ovarian cancer. *Epidemiology*. 2016; 27(6):797-802.

these studies (Gertig (2000)) published a follow-up study, with additional data accrual, 10 years later.[152,153] Each of these studies has enrolled large numbers of women who were asked questions about their genital use of talc and were then followed to see if they developed ovarian cancer. Because these women were followed prospectively, these studies are more scientifically credible, as by design they have removed the selection and recall biases of the case-control studies.

The Nurses' Health Study (NHS) enrolled 121,700 registered nurses starting in 1976. Every two years, the women were sent a questionnaire to update, and in 1982, they were asked questions about their perineal exposure to talc.[154] The frequency of use was ascertained by asking women if they were never-users, daily, one to six times per week, or users of talc in the perineal area < 1 day/week. Forty percent of the cohort (31,789 women) reported ever-use of talc. The study cohort was then followed for 14 years. Confirmation of the diagnosis of ovarian cancer was made by obtaining medical records from any of the subjects who reported that they had been diagnosed with the disease. This study found that there was no association between the ever-use of talc in the perineal area and the development of ovarian cancer with a RR of 1.09 (CI 0.86,1.37). The authors also looked at the risk with different histologic subtypes of ovarian cancer and reported a modest increased risk for serous histology with ever-use of talc (RR 1.4; CI 1.02,1.91), but ever-daily use did not show the same statistically significant result (RR 1.49; CI 0.98,2.26), demonstrating the lack of a dose-response curve. Central to the hypothesis that genital talc use causes ovarian cancer is the theory that the talc migrates up to the fallopian tubes and lands on the ovaries. If this is indeed true, then women who used talc and never had a tubal ligation should be at an increased risk of developing ovarian cancer over never-users. To evaluate this hypothesis, the authors performed the analysis on the data after the women with tubal ligations and/or hysterectomies were removed from the data set and found that women who had ever-used talc and had not had a tubal ligation and/or hysterectomy were not at an increased risk of developing ovarian cancer (RR 1.15; CI 0.89,1.49).[155]

The authors of the NHS study published a follow-up study 10 years later.[156] This study did not ask any additional questions on perineal exposure to talc, but it did allow for more time to pass (24 years in total), which improves the potential latency and increased the ovarian cancer case count (from 307 to 797), which should substantiate

[152]Gates MA., et al. Risk factors for epithelial ovarian cancer by histologic subtype. *American Journal of Epidemiology*. 2010; 171:45-53.
[153] Gertig DM., et al. Prospective study of talc use and ovarian cancer. *Journal of the National Cancer Institute*. 2000; 92:249-52.
[154] Gertig DM., et al. Prospective study of talc use and ovarian cancer. *Journal of the National Cancer Institute*. 2000; 92:249-52.
[155] Gertig DM., et al. Prospective study of talc use and ovarian cancer. *Journal of the National Cancer Institute*. 2000; 92:249-52.
[156] Gates MA., et al. Risk factors for epithelial ovarian cancer by histologic subtype. *American Journal of Epidemiology*. 2010; 171:45-53.

any association between talc and the development of ovarian cancer, if one exists. Importantly, the previously reported association between serous cancers and genital talc use did not withstand the test of time, with the association not being statistically significant with the RR 1.06 (CI 0.84,1.35) in this follow-up study. Consistent with the earlier publication, there remained no statistically significant association between using talc perineally > once/week and the development of any histology of epithelial ovarian cancer, even with the passage of an additional 10 years of time and the diagnosis of an additional 490 cases of ovarian cancer (RR 1.06; CI 0.89,1.28). A criticism that has been made of these two studies is that they only ascertained information on talc usage at one point in time. We know from Wu (2015), however, that in women who are ever-users of talc in the perineal area, the mean duration of use is greater than 20 years.[157] Therefore, even though the question regarding the application of talc that was asked in this study was a snapshot in time, the data that were collected on talc application in the perineal area reflected chronic, habitual use with a mean duration of 20 years.

The Women's Health Initiative (WHI) Study collected data from 61,576 women on their use of talc in the genital area and then examined whether or not there was an association with the development of ovarian cancer.[158] The women were asked questions about whether or not they had ever used talc in the genital area, and if they replied yes, they were asked specific questions about the duration of use (<1 year; 1-4 years; 5-9 years; 10-19 years; ≥ 20 years). As cases of ovarian cancer were self-reported, medical records were requested and adjudicated centrally by the WHI. After a mean follow up of 12.4 years, this study reported that there was no statistically significant association between the use of talc in the genital area and the development of ovarian cancer for ever-users (HR 1.13; CI 0.93,1.37), or for women who reported genital use of talc for 20 years or more (HR 1.10; CI 0.82,1.48). Additionally, there was no trend of increased risk with increasing duration of use; women who used talc in the genital area for 10 or more years had a HR of 0.98 (CI 0.75,1.29), while women who used talc for < 9 years had a HR of 1.24 (CI 0.99,1.55), with neither value demonstrating statistical significance. The women who were enrolled in this study were the exact age range of the majority of the women who develop ovarian cancer. Study subjects were 50-79 years old at enrollment with a mean age of 63.3, and as discussed above, the median age of diagnosis of ovarian cancer is 63 years old. Additionally, these women were followed for another 12.4 years, which translates to the study subjects being 62-91 years old at the conclusion of the study. If a disproportionate number of cases of ovarian cancer were going to develop, it would be in this exact population. Plaintiffs' have raised the concern that the use of talc in the genital region is leading to an earlier mean age of ovarian cancer diagnoses. This contention is not supported by the literature. Cramer (2016) reported that talc users, both cases and controls, were more

[157] Wu AH., et al. African Americans and Hispanics remain at lower risk of ovarian cancer than non-Hispanic Whites after considering non-genetic risk factors and oophorectomy rates. *Cancer Epidemiology, Biomarkers & Prevention*. 2015 24(7):1094-100.

[158] Houghton SC., et al. Perineal powder use and risk of ovarian cancer. *Journal of the National Cancer Institute*. 2014; 106(9):208.

likely to be older and in fact 68% of the cases who reported talc use in this study were > 50 years old.[159] Schildkraut (2016) also reported that cases were older than controls in her study with only 5.3% of cases being <40 years old.[160] Lastly, the "latency period" of this study should not be assumed to be the same as the follow-up period of 12.4 years. The latency period is defined as the time from which the women were exposed to the environmental agent, specifically in this case, talc applied perineally, through the entire time of the study period. At the time of the conclusion of the study, the subjects who reported talc use in the genital area for more than 20 years did not demonstrate a statistically significant increased risk of developing ovarian cancer (HR=1.10; CI 0.82,1.48), and they had a purported latency period of 30+ years. The findings from the WHI study are scientifically sound not only because the study examines the age-appropriate population, but also for the long period of time that it reports upon, with the time of exposure to talc beginning many years prior to the time of data collection.

The Sister Study identified 41,654 women between the ages of 35-74 who had a sister diagnosed with breast cancer.[161] The women in this cohort are known to be at a higher risk of developing ovarian cancer, as they have a first-degree relative with breast cancer. The women were then asked about whether or not they had used talc in the genital area between the ages of 10-13 as well as in the 12 months prior to study enrollment. They were also asked about their frequency of use. Cases of ovarian cancer were confirmed by examining either medical records or death certificates. The authors reported that there was no statistically significant association between the perineal use of talc and the development of ovarian cancer (HR 0.73; CI 0.44,1.2). The hazard ratios reported did not change even when the women with BRCA mutations were excluded from the analysis; however, these women represented a small fraction of the study subjects. Although the mean time of follow up in this study was shorter than the other cohorts, and as a result, the purported latency period for this study is shorter than the other studies, the results of this study are still informative. The mean age of the study subjects was 55, with 55% of the controls and 69% of the cases, being postmenopausal. As stated above, this study population is the same age range as the women who develop ovarian cancer in the general population. Additionally, of the women who reported genital use of talc within the prior 12 months, they most likely became regular users of talc around 20 years old, (according to Cramer (2016))[162], meaning that the potential latency period of this study is at least 20+ years.

In January 2020, O'Brien et al. published a prospective pooled analysis with data from 4 large cohort studies: the Nurse's Health Study I (NHS I), Nurse's Health Study II (NHS II),

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[159] Cramer DW., et al. The association between talc use and ovarian cancer: A retrospective case-control study in two US states. *Epidemiology*. 2016; 27(3):334-46.
[160] Schildkraut JM., et al. Association between body powder use and ovarian cancer: the African American Cancer Epidemiology Study (AACES). *Cancer Epidemiology and Prevention Biomarkers*. 2016; cebp-1281.
[161] Gonzalez N., et al. Douching, talc use, and risk of ovarian cancer. *Epidemiology*. 2016; 27(6):797-802.
[162] Cramer DW., et al. The association between talc use and ovarian cancer: A retrospective case-control study in two US states. *Epidemiology*. 2016; 27(3):334-46.

the Sister Study and the Women's Health Initiative (WHI).[163] Importantly, the study subjects from the NHS II data set had not been reported on previously, and the pooled data from the other 3 studies included additional follow up time, further weakening the criticism from plaintiffs' experts that the cohort studies are limited by a short period of follow up. The cohort consisted of 252,745 women with a median age of 57 years and an estimated crude cumulative incidence of ovarian cancer at age 70 years of 1.3%, reflecting the statistics of the general population at risk for ovarian cancer.[164] As the individual cohort studies in the analysis asked different questions, the authors of the pooled analysis extracted the data to examine risk of developing ovarian cancer with respect to "ever" perineal talc exposure, long term exposure (>/20 years) and frequent exposure (>/ 1/week). The authors did not find a statistically significant increased risk of developing ovarian cancer with the perineal application of talc with any of the exposure measures of ever use (HR 1.08; CI 0.99-1.07), frequency (HR 1.09; CI 0.97,1.23) or duration (HR 1.01; CI 0.82-1.25).

Plaintiffs' gynecologic oncology witnesses attempt to discredit the O'Brien (2020) study, raising issues such as the "possibility of [its] being underpowered, the discordance between the findings and the conclusions of the authors, the lack of consistency among the cohort inquiries, and the failure to take into account the age and menopausal status of the subjects," and referring to published "criticisms of the paper [] outlined in Letters to the Editor (from Drs. Cramer, Harlow, Murray, and Rothman)."[165,166] But these criticisms reflect a one-sided approach in which plaintiffs' experts search for flaws in studies that do not support their conclusions, while failing to apply similar scrutiny to studies they view as supportive of their opinions. The O'Brien article included 250,000 women, making it adequately powered (as discussed further below) and was accompanied by an editorial that called its findings "overall reassuring."[167] And while different cohort studies did not make identical inquiries concerning frequency and duration of use,[168] the same is true of the case-control studies that are included in the various meta-analyses on which the experts based their opinions. It is notable that plaintiffs' experts seek to assign essentially zero weight to the O'Brien study based on perceived weaknesses of the study – even though it was published by respected researchers in the highly prestigious Journal of the American Medical Association – basing their dismissive conclusions on letters to the editor that were co-authored by other plaintiffs' experts.

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[163] O'Brien, KM, et al. Association of powder use in the genital area with risk of ovarian cancer. *JAMA.* 2020; 323(1), 49-59.
[164] National Cancer Institute, Surveillance, Epidemiology and End Results Program: *Cancer Stat Facts: Ovarian Cancer* (last accessed May 12, 2024) https://seer.cancer.gov/statfacts/html/ovary.html
[165] Amended Rule 26 Expert Report of Daniel Clarke-Pearson, MD, dated Nov. 15, 2023, p.9.
[166] Amended Rule 26 Expert Report of Judith Wolf, MD dated Nov. 15, 2023, p. 10.
[167] Gossett DR., et al. Use of powder in the genital area and ovarian cancer risk: Examining the evidence. JAMA. 2020 Jan 7;323(1):29-31.
[168] Cramer DW. Comment & Response: Genital Powder Use and Ovarian Cancer. *JAMA*. 2020; 323(20):2095-2096.

Plaintiffs' experts also focus on a subgroup analysis of the O'Brien study, in which women with intact reproductive tracts (no BTL, no hysterectomy) were compared to women who had undergone hysterectomy or prior tubal ligation. The authors reported a statistically significant increased risk of developing ovarian cancer in women who applied talc perineally and had an intact reproductive tract (HR1.13; CI 1.01-1.26) compared to women with prior BTL or hysterectomy. There are several problems with the reliance plaintiffs' experts place on this subgroup analysis. The first is the presumption that women with intact reproductive tracts are a different study population than women with disrupted reproductive tracts with respect to talc exposure. As stated above, most women who apply talc perineally begin to do so in their teens and 20s and continue use for a mean of 20 years. Most women who undergo hysterectomy or BTL, do so once they have completed their childbearing, which is usually in their 30s-40s, the same age at which most women stop applying talc to their perineum.[169,170] There is also statistical evidence that demonstrates that these women are the same study population in terms of hypothetical risk. The homology between women with intact versus interrupted reproductive tracts is demonstrated in the O'Brien paper by the analysis of heterogeneity with a *P* value of 0.15. Thus, any statistically significant finding in this subgroup analysis is faulty because the underlying assumption that they are different study populations in terms of risk is flawed. Gossett (2020) recognizes this point in her editorial, stating "[t]he subgroup analysis suggesting that women with intact reproductive tracts who used powder in the perineal area developed ovarian cancer more frequently than nonusers is below the effect size that epidemiologists generally consider and should not be selectively highlighted by the statistically unsophisticated reader as evidence of a relationship." [171] To be clear, having a tubal ligation decreases the risk of developing ovarian cancer, but there is no evidence that an alteration in risk is caused by a difference in exposure to talc.

Woolen et al (2022) published a paper which they titled as a "systematic review and meta-analysis" on the association between frequent use of perineal talcum powder and ovarian cancer.[172] The authors claim that the results of this paper make a "significant contribution" to the available literature as it is a meta-analysis of ten case-control studies and one cohort study which they claim is O'Brien (2020) but in fact it is actually only the data from NHS1 with the inclusion of previously unpublished data. No other cohort studies are included in this analysis as the authors state those studies (which are included in the full O'Brien analysis) did not meet the inclusion criteria as they did not

[169] Cramer DW., et al. The association between talc use and ovarian cancer: A retrospective case-control study in two US states. *Epidemiology*. 2016; 27(3):334-46.
[170] Wu AH., et al. African Americans and Hispanics remain at lower risk of ovarian cancer than non-Hispanic Whites after considering non-genetic risk factors and oophorectomy rates. *Cancer Epidemiology, Biomarkers & Prevention*. 2015 24(7):1094-100.
[171] Gossett DR., et al. Use of powder in the genital area and ovarian cancer risk: Examining the evidence. JAMA. 2020 Jan 7;323(1):29-31.
[172] Woolen, S, et al. Association between the frequent use of perineal talcum powder products and ovarian cancer: a systematic review and meta-analysis. *J Gen Intern Med*. 2022; 37(10):2526-2532.

report on frequency of use of at least 2 times per week. This data set is manipulated, however, as described in the "Data Extraction" section where the authors report "[w]hen duplicate reports of the same subjects were published, the publication reporting the highest talc use was selected." This statistical manipulation was performed to "obtain as close to daily use as possible." The authors report a summary pooled OR of 1.47 (CI 1.31-1.65) for all ten studies and an OR of 1.49 (1.29-1.72), when the analysis is restricted to the case-control studies. This means the positive OR reported in this study is entirely due to the case-control studies and not at all a reflection of the data contributed by the NHS1 cohort study.

The NCI PDQ expressed skepticism about the Woolen analysis stating "[a] meta-analysis of ten case-control studies and a highly selected subset analysis of one prospective cohort study found an association….[h]owever, because of the structure of this analysis, the results should be interpreted with care."[173] In this situation, and in any circumstance in which subset analyses are performed that are not the intent of the original study hypothesis and design, the interpretation of data should always be suspect.

In 2024, Chang et al. reported on the use of personal care product mixtures and the incidence of hormone-sensitive cancers in the women that were originally recruited for the Sister Study.[174] As in Gonzalez et al. (2016),[175] women were asked about frequency of exposure to any of 41 personal care products (PCPs) in the 12 months prior to study enrollment. The PCPs were grouped into four different categories including beauty products, everyday hair products, hygiene products and skincare products. The women were then followed prospectively for an average of 11.6 years and data on the incidence of breast, ovarian and uterine cancers were collected. The only category that demonstrated a positive association with the development of ovarian cancer was the hygiene category (HR 1.35 (CI 1.00-1.83)), which included the genital application of talc. There was, however, no increased HR specifically for talc with the forest plots for the single product PCPs failing to demonstrate any suggested association or statistical significance with the development of ovarian cancer and the genital application of talc (see Fig 4).[176] The contribution to the increased risk that was found in the hygiene group was attributable to an increased risk from douching with an HR 1.31(CI 1.06-1.62).

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[173] National Cancer Institute, *Ovarian, Fallopian Tube and Primary Peritoneal Cancer Prevention (PDQ): Who is at Risk?* (updated March 6, 2024) https://www.cancer.gov/types/ovarian/hp/ovarian-prevention-pdq#cit/section_1.11.

[174] Chang, C.J., O'Brien K., Keil A., Goldberg M., Taylor K., Sandler D, White A. (2024). Use of personal care product mixtures and incident hormone-sensitive cancers in the Sister Study: A U.S.-wide prospective cohort. *Environment International*, 183:108298.

[175] Gonzalez N., et al. Douching, talc use, and risk of ovarian cancer. *Epidemiology.* 2016; 27(6):797-802.

[176] Chang, C.J., O'Brien K., Keil A., Goldberg M., Taylor K., Sandler D, White A. (2024). Use of personal care product mixtures and incident hormone-sensitive cancers in the Sister Study: A U.S.-wide prospective cohort. *Environment International*, 183:108298 (figure 4).

In a similar study, by several of the same authors and using the same Sister Study subjects, O'Brien et al. (2024), recently reported on the use of intimate care products and the incidence of hormone related cancers - breast, ovary and uterine cancers.[177] In this study, the authors used exposure data from study entry and then again queried the subjects about their exposure in the years 2017- 2019, and reported considerably different results from those originally reported by Gonzalez et al (2016)[178] and Chang et al. (2024).[179] Critically, the authors decided to "correct" and "impute" certain data points - and perform the analysis under various exposure reassignment assumptions - essentially to model what the data may have been - rather than use the actual data collected, to account for missing data and potential recall bias.[180]

A substantial portion of the cohort failed to respond to the 2017 - 2019 follow-up questionnaire and women diagnosed with ovarian cancer in the intervening years were overrepresented within that group. In one approach, the authors used a model to predict how those women might have responded based on a series of predictive co-variates. This model is the primary one from which the authors draw their conclusions. The authors then sought to determine how recall bias might affect these modeled results. For those subjects diagnosed with ovarian cancer who changed their exposure history (or were modeled to change their exposure history) from never use to ever use, the authors assumed that 25% of the subjects were changing their exposure history because of recall bias and recalculated their results. They still found a positive association between talc exposure and the risk of developing ovarian cancer, but one that was substantially reduced.[181] What we know from O'Brien's prior publication (2023)[182] is that recall bias presents a real challenge; the only study subjects that changed their exposure history to an increase in exposure were the subjects that were diagnosed with ovarian cancer. The magnitude of that bias, however, has yet to be defined. It is unclear why the authors settled on a 25% rate of reclassification which yielded a statistically significant HR, whereas had they assumed a 50% reclassification

[177] O'Brien KM, et al. Intimate Care Products and Incidence of Hormone-Related Cancers: A Quantitative Bias Analysis. *J Clin Oncol*. 2024 May 15:JCO2302037. doi: 10.1200/JCO.23.02037. Epub ahead of print. PMID: 38748950.

[178] Gonzalez N., et al. Douching, talc use, and risk of ovarian cancer. *Epidemiology.* 2016; 27(6):797-802.

[179] Chang, C.J., O'Brien K., Keil A., Goldberg M., Taylor K., Sandler D, White A. (2024). Use of personal care product mixtures and incident hormone-sensitive cancers in the Sister Study: A U.S.-wide prospective cohort. *Environment International*, 183:108298.

[180] O'Brien KM, et al. Intimate Care Products and Incidence of Hormone-Related Cancers: A Quantitative Bias Analysis. *J Clin Oncol*. 2024 May 15:JCO2302037. doi: 10.1200/JCO.23.02037. Epub ahead of print. PMID: 38748950.

[181] O'Brien KM, et al. Intimate Care Products and Incidence of Hormone-Related Cancers: A Quantitative Bias Analysis. *J Clin Oncol*. 2024 May 15:JCO2302037. doi: 10.1200/JCO.23.02037. Epub ahead of print. PMID: 38748950.

[182] O'Brien KM., et al. Douching and genital talc use: patterns of use and reliability of self-reported exposure. *Epidemiology.* 2023; 34(3): 376-384.

the findings would not have demonstrated such an association (Figure 2, O'Brien 2024).[183]

A criticism that is often made of the cohort studies is that they are not sufficiently powered to detect a modest increase in risk. This assertion is simply unsubstantiated by the actual science. In Berge (2018), the authors performed separate meta-analyses by study design (case-control vs. cohort) and were able to demonstrate that "the statistical power of the meta-analysis of these cohort studies to detect a RR of 1.25, similar to the result of the meta-analysis of case-control studies, was 0.99. Thus, low power of cohort studies cannot be invoked as [an] explanation of the heterogeneity of results."[184] This finding by Berge that the cohorts are sufficiently powered in a meta-analysis preceded the publication of the O'Brien (2020) pooled analysis. It is notable that in both Penninkilampi and Berge, when the data from the case-control studies were analyzed separately from the pooled cohort data, only the analysis from the case-control studies showed a statistically significant increase in risk, with the cohort studies not demonstrating such an association, whether or not the data from the Gates study was omitted, as was the case in the Penninkilampi study.[185,186]

Collectively the cohort studies do not demonstrate any statistically significant, consistent association between the genital or perineal use of talc and an increased risk of developing ovarian cancer. The only cohort study that did report a statistically significant HR is the O'Brien et al. (2024) study, which by design is a manipulated data set with exposure reassignment assumptions. All of these studies contained information on years of exposure or frequency of use and there is no evidence from any of these studies of a dose-response curve with either longer periods of use or more perineal applications of talc. The risk of ovarian cancer did not increase with more exposure, as we would expect to see with any environmental agent that is thought to have a causative role in the development of a cancer.

Meta-Analyses and Pooled Analyses

Several meta-analyses have been published on the proposed relationship between the perineal application of talc and the development of ovarian cancer. In addition, there have been a few published pooled analyses; two are independent and another is found

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[183] O'Brien KM, et al. Intimate Care Products and Incidence of Hormone-Related Cancers: A Quantitative Bias Analysis. *J Clin Oncol*. 2024 May 15:JCO2302037. doi: 10.1200/JCO.23.02037. Epub ahead of print. PMID: 38748950.

[184] Berge W., et al. Genital use of talc and risk of ovarian cancer: a meta-analysis. *European Journal of Cancer Prevention*. 2018; 27(3):248-57.

[185] Berge W., et al. Genital use of talc and risk of ovarian cancer: a meta-analysis. *European Journal of Cancer Prevention*. 2018; 27(3):248-57.

[186] Penninkilampi R., et al. Perineal talc use and ovarian cancer: A systematic review and meta-Analysis. *Epidemiology*. 2018; 29(1):41-9.

within the discussion sections of one of the case-control studies).[187,188,189] The majority of these studies combine the data from any number of the previously published case-control studies in an attempt to demonstrate a more robust and statistically significant association. More recently, three of the meta-analyses have added data from three of the cohort studies.[190,191,192] Absent from the Penninkilampi paper, however, are the data from Gates (2010), which is the ten-year follow-up data from the original NHS publication by Gertig (2000). The authors fail to disclose why they chose to include the earlier study (Gertig 2000) over the later (Gates 2010) when the later study clearly has the potential to accrue more cases, an increased purported latency period and more statistical relevance.

As stated previously, since the meta-analyses and pooled analyses are essentially compilations of the original publications, they are subject to the same weaknesses and biases that were embedded in the smaller original studies. As the authors in Penninkilampi acknowledge "a limitation of this study is that it pools nonrandomized studies, primarily case-control studies. The retrospective nature of case-control studies introduces the potential for recall bias. In this case, it is entirely possible that patients with ovarian cancer may be more aware of their previous talc use and hence be more likely to report higher past use."[193]

Additionally, because not all of these original case-control and cohort studies were conducted in the same manner, or asked the study subjects the exact same questions, the merging of the data presents some quality problems (the same issue that plaintiffs' experts raise in connection with the O'Brien (2020) study, as noted above, even though the O'Brien (2020) analysis pools far fewer studies and thus implicates far less variability in the usage inquiries).

The dominance of data from case-control studies also poses significant problems. This exact issue was raised in the Taher manuscript, where the authors applied the GRADE framework "to assess the quality of the evidence derived from the studies included" in

[187] Cramer DW., et al. Genital talc exposure and risk of ovarian cancer. *International Journal of Cancer*. 1999; 81(3):351-6.
[188] Langseth H., et al. Perineal use of talc and risk of ovarian cancer. *Journal of Epidemiology and Community Health*. 2008; 62(4):358-60.
[189] Terry KL., et al. Genital powder use and risk of ovarian cancer: A pooled analysis of 8,525 cases and 9,859 controls. *Cancer Prevention Research*. 2013; 6(8):811-21.
[190] Berge W., et al. Genital use of talc and risk of ovarian cancer: a meta-analysis. *European Journal of Cancer Prevention*. 2018; 27(3):248-57.
[191] Penninkilampi R., et al. Perineal talc use and ovarian cancer: A systematic review and meta-Analysis. *Epidemiology*. 2018; 29(1):41-9.
[192] Taher M., et al., Critical Review of the Association between Perineal Use of Talc Powder and Risk of Ovarian Cancer. *Reproductive Toxicology*. 2019; 90:88-101.
[193] Penninkilampi R., et al. Perineal talc use and ovarian cancer: A systematic review and meta-Analysis. *Epidemiology*. 2018; 29(1):41-9.

their review.[194] The authors reported that "the evidence derived from the observational studies in this review was initially classified as being of low certainty within the GRADE framework; this was further downgraded to very low certainty in light of the risk of bias" which was "mainly due to the potential for recall bias in the included case control studies."

When considered as a group, the meta-analyses and pooled analyses report modest increases in the risk of developing ovarian cancer with the genital use of talc in the range of an odds ratio of 1.24 to 1.4. Because this is exactly the range that is reported in the case-control studies that report a positive association, grouping the studies together did not lead to any more strength in association. This finding is no great surprise since several of the meta-analyses used many of the same case-control studies in their analyses. The earliest meta-analysis is a composite of six studies published in 1992.[195] In 1995, Gross and Berg published another meta-analysis that used all six of the studies from the 1992 study and added three more, but then in 1999, these nine studies were re-hashed into another meta-analysis with an additional five studies.[196,197] With the more recent publications of Penninkilampi and Berge, the percentage of overlapping studies is even higher.[198,199] Both studies analyzed 24 case-control studies, 19 of which they share in common. In fact, as detailed in the section on the cohort studies above, the meta-analyses that included the cohort data not only further substantiated how weak the overall association is, but also how inconsistent the association is, as none of the cohort studies demonstrated a statistically significant association, either independently or grouped in the meta-analyses.[200,201] Additionally, as extensively discussed in the Taher study, the quality of the evidence in these meta-analyses is considered to be of "very low certainty" due to the inherent biases found in the included case control studies.[202]

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[194] Taher M., et al., Critical Review of the Association between Perineal Use of Talc Powder and Risk of Ovarian Cancer. *Reproductive Toxicology*. 2019; 90:88-101.

[195] Harlow BL., et al. Perineal exposure to talc and ovarian cancer risk. *Obstetrics & Gynecology*. 1992; 80:19-26.

[196] Gross AJ., et al. A meta-analytical approach examining the potential relationship between talc exposure and ovarian cancer. *Journal of Exposure Analysis and Environmental Epidemiology*. 1995; 5(2):181-95.

[197] Cramer DW., et al. Genital talc exposure and risk of ovarian cancer. *International Journal of Cancer*. 1999; 81(3):351-6.

[198] Penninkilampi R., et al. Perineal talc use and ovarian cancer: A systematic review and meta-Analysis. *Epidemiology*. 2018; 29(1):41-9.

[199] Berge W., et al. Genital use of talc and risk of ovarian cancer: a meta-analysis. *European Journal of Cancer Prevention*. 2018; 27(3):248-57.

[200] Berge W., et al. Genital use of talc and risk of ovarian cancer: a meta-analysis. *European Journal of Cancer Prevention*. 2018; 27(3):248-57.

[201] Penninkilampi R., et al. Perineal talc use and ovarian cancer: A systematic review and meta-Analysis. *Epidemiology*. 2018; 29(1):41-9.

[202] Taher M., et al., Critical Review of the Association between Perineal Use of Talc Powder and Risk of Ovarian Cancer. *Reproductive Toxicology*. 2019; 90:88-101.

Lack of Support for a Dose-Response Curve across the Epidemiologic Literature

A dose-response, or biologic gradient, refers to an exposure-response relationship whereby with increasing exposures, the magnitude of the response will be even greater. In the case of genital use of talc and the development of ovarian cancer, this relationship is not borne out in the literature. Four studies that are frequently cited by plaintiffs as supportive evidence of a dose-response relationship between the perineal application of talc and the development of ovarian cancer include Terry (2013), Penninkilampi (2018), Schildkraut (2016) and Cramer (2016). But not one of these studies actually demonstrate such a relationship.[203,204,205,206]

Terry (2013) is a pooled analysis of eight case-control studies in which the only significant finding was a comparison of ever use with never use. The authors report that "although a significant increase in risk with an increasing number of genital powder applications was found for nonmucinous epithelial ovarian cancer when nonusers were included in the analysis, no trend in cumulative use was evident in analyses restricted to ever-users of genital powder. Taken together, these observations suggest that the significant trend test largely reflects the comparison of ever-regular use with never use."[207]

Penninkilampi (2018) utilized only 5/24 of the case-control studies and none of the cohort studies they claimed were included in their meta-analysis to examine what they called a dose-response gradient. In this analysis, they examined the risk of developing ovarian cancer with <3600 total lifetime applications and compared it to >3600 applications. The authors reported a modest increased risk of ovarian cancer with <3600 applications (OR 1.32; CI 1.15,1.50), but this number was not statistically significantly different from the OR reported for ≥ 3600 applications (OR 1.42; CI 1.25,1.61) because the confidence intervals overlap. By definition, there is no dose-response gradient if the risk does not change with increasing exposure.[208]

Schildkraut (2016) is a population-based case-control study that also examined risk as defined by <3600 applications vs. ≥ 3600 applications in addition to examining the differences in risk with exposure < 20 years vs. ≥ 20 years. The women exposed to talc for < 3600 applications or for < 20 years did not have a statistically significant increased

[203] Terry KL., et al. Genital powder use and risk of ovarian cancer: A pooled analysis of 8,525 cases and 9,859 controls. *Cancer Prevention Research*. 2013; 6(8):811-21.
[204] Penninkilampi R., et al. Perineal talc use and ovarian cancer: A systematic review and meta-Analysis. *Epidemiology*. 2018; 29(1):41-9.
[205] Schildkraut JM., et al. Association between body powder use and ovarian cancer: the African American Cancer Epidemiology Study (AACES). *Cancer Epidemiology and Prevention Biomarkers*. 2016; cebp-1281.
[206] Cramer DW., et al. The association between talc use and ovarian cancer: A retrospective case-control study in two US states. *Epidemiology*. 2016; 27(3):334-46.
[207] Terry KL., et al. Genital powder use and risk of ovarian cancer: A pooled analysis of 8,525 cases and 9,859 controls. *Cancer Prevention Research*. 2013; 6(8):811-21.
[208] Penninkilampi R., et al. Perineal talc use and ovarian cancer: A systematic review and meta-Analysis. *Epidemiology*. 2018; 29(1):41-9.

risk of developing ovarian cancer. This means that in comparing the women with fewer exposures to the women with ≥ 3600 total applications or exposure for ≥ 20 years, the comparison being made is essentially never users to ever users and does not constitute a dose-response gradient.[209] This is essentially the same confounding observation pointed out by Terry (2013), whereby without a trend in cumulative use, the statistically significant finding at ≥ 3600 total applications or exposure for ≥ 20 years and not at lower doses, is really just a reflection of a comparison between never with ever users and does not demonstrate a dose-response gradient.[210] Recently, Davis (2021) used data from five studies to report on the risks of ovarian cancer in African American women as compared with Caucasian women as genital powder use is more common among African American women. As stated earlier, the findings for African American women showed no statistically significant increased risk and the authors report that while different from the Schildkraut (2016) study, "our results are consistent with most prior studies that report no significant dose-response association between genital powder use and ovarian cancer risk."[211] It is notable that Dr. Schildkraut is a co-author on this study.

Cramer (2016) is a case-control study that pooled data from three separate prior enrollment phases. The study collected data on frequency of talc use in terms of number of days used per month and months per year as well as duration data by number of years used. The authors also made calculations to estimate number of lifetime applications from the frequency and duration data. The authors reported an increasing risk with an increased number of days used per month. The data on increasing risk and number of years used, however, was flat, with the risk for < 8 years (OR 1.31; CI 1.03,1.68) being the same as the risk for > 35 years (OR 1.33; CI 1.03, 1.71) (Table 1 from Cramer (2016).[212]

[209] Schildkraut JM., et al. Association between body powder use and ovarian cancer: the African American Cancer Epidemiology Study (AACES). *Cancer Epidemiology and Prevention Biomarkers*. 2016; cebp-1281.
[210] Terry KL., et al. Genital powder use and risk of ovarian cancer: A pooled analysis of 8,525 cases and 9,859 controls. *Cancer Prevention Research*. 2013; 6(8):811-21.
[211] Davis CP., et al. Genital powder use and risk of epithelial ovarian cancer in the Ovarian Cancer in Women 2 of African Ancestry Consortium. *Cancer Epidemiology and Prevention Biomarkers*. 2021; 30(9)1660-1668.
[212] Cramer DW., et al. The association between talc use and ovarian cancer: A retrospective case-control study in two US states. *Epidemiology*. 2016; 27(3):334-46.

ORIGINAL ARTICLE

OPEN

The Association Between Talc Use and Ovarian Cancer

A Retrospective Case–Control Study in Two US States

Daniel W. Cramer,[a,b] Allison F. Vitonis,[a] Kathryn L. Terry,[a,b] William R. Welch,[c] and Linda J. Titus[d]

Background: Multiple studies of ovarian cancer and genital talc use have led only to ... greater clarity

Conclusion: Risks for epithelial ovarian cancer from genital talc use vary by histologic subtype, menopausal status at diagnosis, HT use,

TABLE 1. Type, Timing, and Duration of Genital Talc Use

Frequency of use			
No genital use	1,551 (74)	1,399 (69)	1.00 (referent)
1–7 days per month	220 (11)	227 (11)	1.17 (0.96, 1.44)
8–29 days per month	110 (5)	133 (7)	1.37 (1.05, 1.78)
≥30 days per month	205 (10)	267 (13)	1.46 (1.20, 1.78)
P trend			<0.0001
Years used			
Never used	1,551 (74)	1,399 (69)	1.00 (referent)
<8	133 (6)	152 (8)	1.31 (1.03, 1.68)
8–19	126 (6)	145 (7)	1.31 (1.02, 1.68)
20–35	147 (7)	178 (9)	1.35 (1.07, 1.70)
>35	129 (6)	152 (7)	1.33 (1.03, 1.71)
P trend			0.002
Months per year of use[c]			
No genital use	1,551 (83)	1,399 (80)	1.00 (referent)
1–3 months per year	61 (3)	60 (3)	1.11 (0.77, 1.61)
4–11 months per year	55 (3)	56 (3)	1.13 (0.77, 1.66)
12 months per year	193 (10)	229 (13)	1.35 (1.09, 1.67)
P trend			0.006

The most inconsistent finding from this study, however, which actually refutes the claim of the existence of a dose-response curve, comes from the fact that data examining "Total genital talc applications" are inconsistent, and conflict with the data presented on "Years used":

TABLE 1. (*Continued*)

	Control Subjects N (%)	Case Subjects N (%)	Adjusted[a] OR (95% CI)
Total genital talc applications (apps) among only those who reported months per year of use[c]			
No genital use	1,551 (83)	1,399 (80)	1.00 (referent)
≤360 apps (equivalent to 1 year of daily use)	106 (6)	103 (6)	1.10 (0.83, 1.47)
361–1,800 apps (equivalent to >1–5 years of daily use)	79 (4)	96 (5)	1.38 (1.01, 1.88)
1,801–7,200 apps (equivalent to >5–20 years of daily use)	61 (3)	63 (4)	1.16 (0.80, 1.66)
>7,200 apps (equivalent to >20 years of daily use)	63 (3)	83 (5)	1.49 (1.06, 2.10)
P trend			0.02
Total genital talc applications among all (assuming 12 months/year when missing months per year of use)			
No genital use	1,551 (74)	1,399 (69)	1.00 (referent)
≤360 apps (equivalent to 1 year of daily use)	138 (7)	138 (7)	1.15 (0.89, 1.47)
361–1,800 apps (equivalent to >1–5 years of daily use)	124 (6)	148 (7)	1.36 (1.06, 1.75)
1,801–7,200 apps (equivalent to >5–20 years of daily use)	124 (6)	156 (8)	1.41 (1.10, 1.80)
>7,200 apps (equivalent to >20 years of daily use)	149 (7)	185 (9)	1.39 (1.11, 1.75)
P trend			0.003

In this paper, the authors calculated a figure for what they called lifetime exposure by multiplying frequency of applications per month by months used. They then divided this number by 360 to yield what they called "talc-years" and reported this along with the number of total genital applications. As seen in Table 1 of the Cramer (2016) study above, this analysis demonstrated that one year of daily use was not statistically significant for increasing the risk of ovarian cancer; > 1-5 years of daily use has a statistically significant increased risk, but with >5-20 years of use, the risk of developing ovarian cancer went down and was not statistically significant and then with >20 years of use, the risk went up and became significant again. This study also includes conflicting and inconsistent data, as in one section of Table 1, 8-19 years of use is shown to increase the risk of developing ovarian cancer, but later in the same table, 5-20 years of talc use, as calculated from total applications, does not demonstrate a statistically significant increase in risk.[213] Cramer (2016) does not establish the existence of a dose-response curve and it actually refutes the possibility of a threshold dose; as does all of the epidemiologic literature cited above.

Summary of the Epidemiologic Literature

The epidemiologic literature on the potential association between the use of talc in the genital area and the development of ovarian cancer does not support a causal role for talc. As discussed above, 52% of the case-control studies did not show a statistically significant increased odds ratio of developing ovarian cancer with the genital use of talc, and in those studies that did have statistically significant findings, the odds ratio was at most a weak association in the range of 1.3-1.5 (Table 1). The findings in these studies are inconsistent, both between studies and within individual studies, and they are unable to demonstrate a dose-response curve, nor a threshold dose. Adding to the lack of consistency in the published literature are the cohort studies, which do not demonstrate any statistically significant associations across the tens of thousands of women studied over decades, except in one study that randomly reassigned exposure categories years after the original data was collected. Excepting O'Brien et al. (2024), the cohort studies, are far less subject to recall bias as they only enquire about exposures prior to ovarian cancer diagnosis, and they do not demonstrate any meaningful association between the genital application of talc and an increased risk of developing ovarian cancer.

Lastly, the meta-analyses bring nothing new to the discussion, again rehashing the same data many times over, without demonstrating any changes in the purported strength of association or any evidence of a dose-response curve. Importantly, none of the studies reported positive findings for any increasing length of time of use (be it duration, or frequency or increasing number of lifetime applications), and they could only achieve a weak statistically significant increase in risk for ever-users compared to never-users that

[213] Cramer DW., et al. The association between talc use and ovarian cancer: A retrospective case-control study in two US states. *Epidemiology*. 2016; 27(3):334-46.

pertained only to the pooling of the case-control studies, and not the cohort studies.[214,215,216]

Migration of Talc from the Perineum to the Ovaries

Integral to the hypothesis that genital application of talc causes ovarian cancer is the theory that talc can migrate from the perineum to the ovaries. Plaintiffs make this assertion as a given, and even the U.S. Food & Drug Administration has stated, "While there exists no direct proof of talc and ovarian carcinogenesis, the potential for particulates to migrate from the perineum and vagina to the peritoneal cavity is indisputable."[217] However, there are many barriers between the external female genitalia and the ovaries, all intentionally evolved to keep the endometrial cavity and the peritoneal cavity (where the ovaries reside) sterile and separate from the non-sterile external environment. For any particulate matter to reach the ovaries from the perineum, it would need to get past the labia majora (which are naturally opposed and close off the inner vestibule). The particle would then need to pass between the opposed labia minora, across the perineal body, through the introitus, up into the vagina and traverse the 7-9 cm of the vagina, and all the while not be washed away by vaginal secretions. From there, the particle would need to navigate into the cervical canal through an opening that is less than 1 cm in diameter and then travel the length of 4-5 cm through the tenacious cervical mucous, before arriving at the endometrial cavity. Once in the endometrial cavity, the particle would then need to travel across 5 cm or so, the length of the uterus, and into the less than 1 cm opening (ostia) of the fallopian tube, travel the entire length of the fallopian tube (10-13 cm) to the fimbria and then land on the ovaries. The female genitalia are designed to prevent such an ascension, as it is important to every woman's health that multiple barriers be in place to prevent easy passage of foreign substances on a regular basis. The female genitalia are not simply open to the external environment. Furthermore, the hypothesis that retrograde ascension is the pathway by which the talc is gaining access to the ovaries is purely speculative and there is no data to support it.

Often cited as support for this unsubstantiated hypothesis of migration is the finding by Heller (1996) of talc particles in the ovaries of 12 women who reported perineal use of talc.[218] The problem with this logic is that talc was also found in the ovaries of 12

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[214] Berge W., et al. Genital use of talc and risk of ovarian cancer: a meta-analysis. *European Journal of Cancer Prevention*. 2018; 27(3):248-57.
[215] Penninkilampi R., et al. Perineal talc use and ovarian cancer: A systematic review and meta-Analysis. *Epidemiology*. 2018; 29(1):41-9.
[216] Terry KL., et al. Genital powder use and risk of ovarian cancer: A pooled analysis of 8,525 cases and 9,859 controls. *Cancer Prevention Research*. 2013; 6(8):811-21.
[217] Food and Drug Administration Letter from Musser SM to Epstein SS Re: Docket Numbers 94P-0420 and FDA-2008-P-0309-0001/CP. Date stamped: April 1, 2014. FDA Denial of 1994 and 2008 Petitions.
[218] Heller DS., et al. The relationship between perineal cosmetic talc usage and ovarian talc particle burden. *American Journal of Obstetrics & Gynecology*. 1996; 174:1507-10.

women who reported never using talc in the perineal area, and the talc counts did not at all correlate with the reported exposure history. The control subjects in this report, the women who actually never used talc, were also found to have talc in their ovaries. This is a failed experiment. No one actually knows how the talc that is found in pathology samples got there. The presumption is that because some researchers have conducted studies whereby they have placed particulate matter into the vagina, be it carbon particles or radio-labeled albumin microspheres, and later found evidence of these substances in the ovaries, talc must be able to migrate from the perineum to the ovaries as well.[219,220] But the vagina is not the perineum and the female genital tract is not an open conduit, and these studies have been conducted in a manner not at all analogous to how women actually apply talc to the perineum.

As additional support for the hypothesis that talc can migrate from the perineum to the ovaries, plaintiffs' experts also often cite a study published in 1961 by Drs. Egli and Newton.[221] In this study, three women were placed under general anesthesia and positioned in a lithotomy position with their legs separated and raised above their bodies and their heads tilted downward from the horizontal. A speculum was placed into the vagina in order to open it and a slurry of carbon particles was inserted into the posterior vagina. The women were given oxytocin injections to induce uterine contractions. The women then underwent surgery to remove their fallopian tubes, which were inspected for the carbon particles. Carbon was found in the tubes of two of the three women and no carbon was identified in the tubes of the third woman. The conditions under which the women in the Egli study were evaluated are not at all analogous to women placing talc on their perineum. The perineum is the external genitalia, and the vagina is an internal organ that is not exposed to the external environment. Women placing talc on their perineum is not at all analogous to a slurry being placed into a woman's posterior vagina via a speculum while she lies on her back with her legs up in the air under general anesthesia. There is absolutely no surge in uterine contractions occurring while a woman dusts her perineum with talc akin to the contractions induced by the oxytocin injections that were given to the women in this study. The experimental design of this study (and of all the studies that are erroneously cited in support of the theory of perineal migration to the ovaries) is artificial and not at

[219] Egli GE., et al. The transport of carbon particles in the human female reproductive tract. *Fertility and Sterility*. 1961; 12(2):151-5.
[220] Venter PF., et al. Migration of particulate radioactive tracer from the vagina to the peritoneal cavity and ovaries. *South African Medical Journal*. 1979; 55(23):917-9.
[221] Egli GE., et al. The transport of carbon particles in the human female reproductive tract. *Fertility and Sterility*. 1961; 12(2):151-5.

all analogous to the real life perineal application of talc.[222,223,224,225] Not a single human study has ever been published that has actually documented the migration of particulate matter from the perineum through the entire female reproductive tract to the ovary.

In recent years, plaintiffs' experts have published new work that ostensibly lends new support to the theory that externally applied talcum powder can reach the ovaries.[226, 227] In McDonald (2019a), for example, the authors (including plaintiffs' expert John Godleski) reported finding talc in pelvic organ sites in five case studies after the adoption of methods intended to reduce the risk of laboratory contamination. But there are several limitations that make it impossible to draw any conclusions from this study. Most critically, the methods adopted for minimizing contamination were undertaken after the tissue was embedded in paraffin – meaning that nothing was done to mitigate the risk of contamination at the point of harvesting and preserving the tissue. Moreover, the authors also reported findings of birefringent materials generally and talc specifically in the control patients, the data for whom was oddly tucked away in a supplementary table only available online (and not in the published version of the paper). The question this study fails to answer is whether externally applied talc can migrate up through the reproductive system to the ovaries.

Inflammation as the Mechanism by which Talc Induces Ovarian Cancer

Several hypotheses have been proposed as to what leads to malignant transformation in the ovary. The incessant ovulation hypothesis suggests that the chronic disruption of the surface of the ovary by the process of ovulation can cause enough damage to the surface epithelium that the cells become cancerous.[228] Others have proposed that it is not the actual disruption that leads to the malignant transformation, but rather the entrapment of the surface epithelium into crypts deep within the ovarian stroma and the epithelium's subsequent exposure to high hormone levels, including estrogens, that is carcinogenic. In litigation, plaintiffs' experts have proposed that talc causes chronic inflammation, which leads to the development of ovarian cancer. The epidemiologic

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[222] De Boer CH. Transport of particulate matter through the human female genital tract. *Reproduction*. 1972; 28(2):295-7.
[223] Egli GE., et al. The transport of carbon particles in the human female reproductive tract. *Fertility and Sterility*. 1961; 12(2):151-5.
[224] Sjosten AC. Retrograde migration of glove powder in the human female genital tract. *Human Reproduction*. 2004; 19(4):991-5.
[225] Venter PF., et al. Migration of particulate radioactive tracer from the vagina to the peritoneal cavity and ovaries. *South African Medical Journal*. 1979; 55(23):917-9.
[226] McDonald SA., et al. Migration of talc from the perineum to multiple pelvic organ sites: five case studies with correlative light and scanning electron microscopy. *American Journal of Clinical Pathology*. 2019; 152(5):590-607.
[227] McDonald SA., et al. Correlative polarizing light and scanning electron microscopy for the assessment of talc in pelvic region lymph nodes. *Ultrastructural Pathology*. 2019; 43(1):13-27.
[228] Fathalla MF. Incessant ovulation-a factor in ovarian neoplasia. *Lancet*. 1971; 2(7716):163.

and biologic data, however, do not support the hypothesis that chronic inflammation plays a role in causing ovarian cancer.

First, as a practicing gynecologic oncologist for 25 years, I have a great deal of experience operating on patients with ovarian cancer. I do not see evidence of an inflammatory process when I am operating on patients with high grade serous ovarian cancer. There is no evidence on microscopic examination of the tissues of granulomas or foreign body giant cell reactions, which are present when the body invokes a chronic inflammatory cascade in response to a foreign substance such as talc. When asked in deposition, plaintiffs' expert Dr. Clarke-Pearson confirmed that it is his position that talc induces an inflammatory response that does not manifest itself in pain, or in macrophage activity that can be seen under a light microscope.[229] Plaintiffs' expert Dr. Judith Wolf testified similarly.[230] Needless to say, inflammation that is undetectable cannot be substantiated by scientific research, and this testimony is speculation not science. Simply, both of these plaintiffs' experts are saying that the inflammation occurs, but they have no way of demonstrating it.

Second, pelvic inflammatory disease (PID) is not associated with the development of invasive high grade serous ovarian cancer. PID is a condition whereby the uterus, tubes and ovaries are involved in an inflammatory response as a result of a sexually transmitted disease that ascends the upper genital tract after sexual intercourse. The inflammatory response can result in abscess formation, development of scar tissue and infertility. Proponents of the hypothesis that ovarian cancer results from chronic inflammation have examined the relationship between PID and the development of ovarian cancer. A few small studies have reported inconsistent results in the past. Rasmussen et al. published a large pooled analysis of 13 case-control studies involving 11,966 women with invasive and borderline ovarian tumors.[231] This study demonstrated no association between a history of PID and ovarian cancer risk (OR=0.99; CI 0.83-1.19) and only women with at least two reported episodes of PID had a two-fold increased risk of borderline tumors. More recently, Piao et al. (2020), published a meta-analysis of 16 previously published studies and reported a positive association between a history of PID and the risk of ovarian cancer with a HR=1.18 (CI 1.13,1.22) with moderate heterogeneity.[232] Importantly in this study, tests of heterogeneity on subpopulations revealed that only the studies restricted to Asian patients and patients with non-serous and borderline carcinomas had a low level of heterogeneity. All of the other studies' populations had high heterogeneity, meaning that there was a great deal of diversity amongst these studies, calling into question whether or not it is meaningful

[229] August 27, 2021 Deposition Transcript of Daniel Clarke-Pearson, MD, pp. 629-630.
[230] September 14, 2021 Deposition Transcript of Judith Wolf, MD, pp. 555-556.
[231] Rasmussen CB., et al. Pelvic inflammatory disease and the risk of ovarian cancer and borderline ovarian tumors: A pooled analysis of 13 case-control studies. *American Journal of Epidemiology*. 2017; 185(1):8-20.
[232] Piao J., et al. Association between pelvic inflammatory disease and risk of ovarian cancer: An updated meta-analysis. *Gynecologic Oncology* 2020; 157(2), 542-548.

to group them into a pooled or meta-analysis. Ultimately, the strongest findings from this paper were consistent with the Rasmussen study where PID is only associated with an increased risk of developing non-serous and borderline tumors of the ovary. This lack of association between a chronic inflammatory condition such as PID and ovarian cancer demonstrates the lack of clinical data to support inflammation as the mechanism of malignant transformation in the ovary. Additionally, if talc really is migrating across all these intermediary organs and causing chronic inflammation, then we would see evidence of an increased risk of cancers developing in the vagina, the cervix and the endometrium – and we do not.

Third, if talc induces ovarian cancer by causing chronic inflammation, then studies examining the use of anti-inflammatory agents such as NSAIDs and aspirin should show a consistent decrease in the risk of developing ovarian cancer with regular use of these agents. The epidemiologic literature that has examined this question has not shown a consistent reduction in the risk of ovarian cancer with the use of NSAIDs, and this includes studies that also examined the risk of perineal application of talc.[233,234] In the Nurses' Health Study (2018), results on the use of analgesics and the risk of ovarian cancer demonstrated inconsistency in terms of dose response as low-dose aspirin appears to decrease the risk of developing ovarian cancer, whereas standard dosing demonstrates no association and the use of non-aspirin NSAIDs actually showed an increased risk of developing ovarian cancer, although not statistically significant.[235] Similarly, a 2019 study pooled data from 13 prospective cohort studies and reported mixed results – a 10% reduction in ovarian cancer risk for daily users of aspirin, but only for 10 years of use (after which the risk was null or even slightly elevated), and no risk relationship between use of other NSAIDs or acetaminophen and ovarian cancer risk.[236] Hurwitz et al. (2022) published a study that examined frequent aspirin use (defined as >/6 days for >/6 months) and the impact on the development of ovarian cancer in patients with risk factors for the disease (endometriosis, obesity, family history, nulliparity, OCP use and BTL).[237] They reported an overall reduction in risk of 13%, although importantly, there was no association found in women with endometriosis, which is often described as an inflammatory process, and specifically there was no effect modification for endometrioid or clear cell tumors, the two histotypes that are known to be associated with endometriosis. By extension, (and as discussed above in the section on endometriosis) the clear cell and endometrioid cancers that develop from

[233]Cramer DW., et al. Over-the-counter analgesics and risk of ovarian cancer. *The Lancet*. 1998; 351(9096):104-7.
[234] Wu AH., et al. Markers of inflammation and risk of ovarian cancer in Los Angeles County. *International Journal of Cancer*. 2009; 124:1409-15.
[235] Barnard ME., et al. Association of analgesic use with risk of ovarian cancer in the Nurses' Health Studies. *JAMA Oncology*. 2018; 4(12):1675-82.
[236] Trabert, B., et al. Analgesic use and ovarian cancer risk: an analysis in the Ovarian Cancer Cohort Consortium. *Journal of the National Cancer Institute* 2019; 111(2): 137-145.
[237] Hurwitz LM, et al. Modification of the Association Between Frequent Aspirin Use and Ovarian Cancer Risk: A Meta-Analysis Using Individual-Level Data From Two Ovarian Cancer Consortia. *J Clin Oncol*. 2022;40(36):4207-4217.

endometriosis likely do not develop as a result of inflammatory processes, but rather through a separate cascade of molecular aberrations.
NSAIDs are active, at least in part, through inhibition of cyclooxygenase (COX) enzymes, whose downstream effects include inflammation and cellular proliferation. Penninkilampi (2018) offers that NSAIDs may be ineffective in decreasing the risk of ovarian cancer because "human epithelial ovarian cells have an unusually low expression of COX-1 and COX-2, which would reduce their sensitivity to the action of NSAIDs."[238] But Penninkilampi (2018) misreports the results from the study they are citing, which was a study on ovarian cancer cells, not normal ovarian epithelium, and the study actually reported finding expression of both COX-1 and COX-2 enzymes in all three cell lines tested, confirming the presence of these proteins with both immunohistochemistry staining and Western blot analysis.[239] More recent publications have validated the above findings, confirming the expression of both COX-1 and COX-2 enzymes in ovarian cancer cells by both immunohistochemistry staining as well as mRNA expression, utilizing a tissue microarray of 190 primary ovarian tumors.[240,241] The gynecologic oncology community does not recommend the use of NSAIDs to patients as a risk-reducing strategy for the development of ovarian cancer as we recommend the use of oral contraceptive agents. The reason that NSAIDs are not recommended is that they have not been shown to be effective in the prevention of ovarian cancer as ovarian cancer is not caused by chronic inflammation.

Moreover, a note on the medical uses of talc seems appropriate to this discussion, as plaintiffs' experts seem to gloss over the important applications of talc, and the inflammatory response it can induce, in the care of women with ovarian cancer.[242] It is not uncommon for women in the advanced stages of disease to develop large pleural effusions which often quickly recur and can make breathing challenging for these patients. Frequently, we recommend these patients undergo procedures such as a thoracentesis (where the fluid is drained from the pleural space) and then follow with a pleurodesis, where talc is sprayed into the space between the layers of the pleura to cause an inflammatory response that is meant to seal the pleural space and prevent the fluid from reaccumulating. The same procedure has been used for other patients such as those with recurrent pneumothorax. Long term follow-up of these patients has never demonstrated any increased rate of malignancy, including mesothelioma, and yet there is extensive evidence of a marked inflammatory response with evidence of fibrosis,

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[238] Penninkilampi R., et al. Perineal talc use and ovarian cancer: A systematic review and meta-Analysis. *Epidemiology*. 2018; 29(1):41-9.
[239] Rodríguez-Burford C., et al. Effects of nonsteroidal anti-inflammatory agents (NSAIDs) on ovarian carcinoma cell lines: preclinical evaluation of NSAIDs as chemopreventive agents. *Clinical Cancer Research*. 2002; 8(1):202-9.
[240] Beeghly-Fadiel A., et al. Differential cyclooxygenase expression levels and survival associations in type I and type II ovarian tumors. *Journal of Ovarian Research*. 2018; 11(1):17.
[241] Wilson AJ., et al. Aberrant over-expression of COX-1 intersects multiple pro-tumorigenic pathways in high-grade serous ovarian cancer. *Oncotarget*. 2015; 6(25):21353.
[242] September 14, 2021 Deposition Transcript of Judith Wolf, MD, p. 540.

foreign body giant cells and the presence of granulomas, confirming that the mechanism of action was through the generation of an inflammatory response.[243]

Korsic (2015) published a most intriguing finding of improved survival in breast and lung cancer patients with malignant pleural effusions who received talc pleurodesis as compared to patients who did not.[244] Median survival was 21.5 weeks in the group receiving pleurodesis and only 9 weeks in the group that did not. The authors hypothesized that talc may have direct antitumor activity. This is supported in part by *in vitro* experiments which have demonstrated that talc induces increased apoptosis and cell death in malignant mesothelial cells, but not in normal pleural mesothelial cells.[245, 246, 247] To this day, talc is still used for pleurodesis in patients with symptomatic pleural effusions because of its ability to generate a chronic inflammatory response with few long term sequelae, including no evidence of neoplastic transformation of normal cells and tissues.

In addition, ACOG recognizes the medical benefits of talc in the care of women receiving gynecologic surgery.[248] In a Committee Opinion first published in January 2015, and then reaffirmed in 2019, ACOG discusses that "postoperative wound complications may be lessened in the obese patient after abdominal hysterectomy with subcutaneous suture placement, **talc application**, or wound vacuums." (bold added) The application of talc into an open superficial surgical wound is intended to engender an inflammatory reaction in response to the presence of a foreign body that would essentially seal the wound and decrease the risk of separation. If ACOG considered talc to be a risk factor for the development of ovarian cancer, it is unlikely that the Committee on Gynecologic Practice would recommend placing it into surgical wounds.

An argument has sometimes been put forth by plaintiff experts that cornstarch powders are safer alternatives than talcum powders. Careful review of the published literature, however, reveals that women who exclusively used perineal cornstarch comprised only ~1% of the study subjects and therefore had no statistical meaning, and certainly no conclusions could be drawn as to the safety or not of perineal application of cornstarch.

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[243]Hunt I., et al. Is talc pleurodesis safe for young patients following primary spontaneous pneumothorax? Interactive Cardiovascular and Thoracic Surgery. 2007; 6(1):117-20.

[244] Korsic M., et al. Talc pleurodesis improves survival of patients with malignant pleural effusions: case-control study. Wiener Klinische Wochenschrift. 2015 Dec 1;127(23-24):963-9.

[245] Nasreen N., et al. Talc induces apoptosis in human malignant mesothelioma cells in vitro. *American Journal of Respiratory and Critical Care Medicine*. 2000 Feb 1;161(2):595-600.

[246] Nasreen N., et al. Talc mediates angiostasis in malignant pleural effusions via endostatin induction [published correction appears in *European Respiratory Journal*. 2007 Jun;29(6):1286. Najmunnisa, N [corrected to Nasreen, N]]. *European Respiratory Journal*. 2007;29(4):761-769.

[247] Lee P., et al. Selective apoptosis of lung cancer cells with talc. Eur. Respir. J. 2010; 3:450-452.

[248] American College of College of Obstetrics and Gynecologists: *Committee Opinion Number 619: Gynecologic Surgery in the Obese Woman.* Published January 2015, reaffirmed 2019. Available from: https://www.acog.org/-/media/project/acog/acogorg/clinical/files/committee-opinion/articles/2015/01/gynecologic-surgery-in-the-obese-woman.pdf.

It is well documented that starch particles can cause adhesions and engender an inflammatory process; hence the reason that the FDA has banned the use of cornstarch on surgical gloves.[249, 250]

Summary

There is no literature showing that particulate matter such as talcum powder, applied to the perineum, can migrate to the ovaries. The link between talc exposure and ovarian cancer is unproven, as there is inconsistency in the detection of talc in the ovarian tissue of women who reported heavy use or no use at all. The clinical and epidemiologic data do not support the hypothesis that talc causes ovarian cancer through the induction of a chronic inflammatory process, primarily because there are no data to support that chronic inflammation is underlying the malignant transformation of the ovarian epithelium at all.

Lack of Data that Talc Induces Carcinogenesis in Ovarian Epithelial Cells

Plaintiffs' experts in this litigation have offered the opinion that there is *in vitro* data and *in vivo* animal data that talc can induce malignant transformation in normal ovarian epithelium. This is pure speculation. Often cited are *in vitro* studies that report that talc can alter cell viability, proliferation and gene expression, but none of these endpoints are an actual demonstration of malignant transformation and can in fact be manifestations of normal cellular responses to any change in the environment.

Buz'Zard reports that treatment of immortalized ovarian epithelial cells results in an increase in cell viability at low doses of talc after 24 hours of incubation; however, there is decreased viability at higher doses and with longer incubation times. [251] These results are hard to reconcile, as any effect of a carcinogenic agent would be expected to demonstrate a dose-response curve. The interpretation is made even more difficult by the fact that there are no controls that are analyzed throughout this study. The same authors also report that talc is able to "transform" the ovarian cells into a malignant phenotype, by demonstrating that the cells treated with talc grow more colonies in soft agar than the untreated cells.[252] The problem here is that the cells are immortalized to begin with and this allows them to grow in soft agar, even without treatment with talc.

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[249] Sjosten AC. Retrograde migration of glove powder in the human female genital tract. *Human Reproduction*. 2004; 19(4):991-5.

[250] Food and Drug Administration. Banned devices; Powdered Surgeon's Gloves, Powdered Patient Examination gloves, and Absorbable Powder for Lubricating a Surgeon's Glove. *Federal Register*. https://www.federalregister.gov/documents/2016/12/19/2016-30382/banned-devices-powdered-surgeons-gloves-powdered-patient-examination-gloves-and-absorbable-powder. Published December 19, 2016. (Last updated September 28, 2022)

[251] Buz'Zard AR., et al. Pycnogenol reduces talc-induced neoplastic transformation in human ovarian cell cultures. *Phytotherapy Research*. 2007; 21(6):579-86.

[252] Buz'Zard AR., et al. Pycnogenol reduces talc-induced neoplastic transformation in human ovarian cell cultures. *Phytotherapy Research*. 2007; 21(6):579-86.

A simple increase in colony counts is not a reflection of "neoplastic transformation," and perhaps is better interpreted as increase in proliferation, and not representative of a malignant process. Lastly, these same authors report on the production of reactive oxygen species (ROS) in cells treated with talc. These results also do not support the hypothesis that talc induces cancer in the treated ovarian epithelial cells. First, the treated ovarian epithelial cells initially show a decrease in production of ROS at 24 hours and then only one dose (50 ug/mL at 120h) demonstrates an increase in ROS above the control cells.[253] Again, there is no demonstration here of a dose-response curve, or even of the induction of a consistent production of ROS, which again is often a reflection of normal cellular function and does not signify malignant transformation.

Another study that is often cited in this litigation is Shukla (2009), wherein mesothelial cells and ovarian cells were treated with varying concentrations of asbestos, nonfibrous talc, titanium dioxide (TiO2) and glass beads and then the cells were examined for viability and changes in gene expression at varying time points.[254] The major findings in this study were actually reported on the asbestos treatments of the mesothelial cells because the results on talc were not at all impressive. The authors reported no changes in viability or gene expression in immortalized ovarian surface epithelial (IOSE) cells treated with talc (which contradicts the findings in Buz'Zard 2007) and also reported that there was only a transient change in gene expression in IOSE treated with low levels of asbestos, as the effects were no longer detectable at 24h.[255] The actual biologic implications of the changes in the gene expression are unknown. None of these findings are consistent with the demonstration of malignant transformation.

Further cited by plaintiffs' experts as evidence that talc is carcinogenic in *in vitro* studies is the study of mouse macrophages in culture treated with talc by Emi et al. (2021).[256,257] The authors treated the macrophages for a 24h time period with either TiO2 as a control, or talc. They then went on to analyze gene expression profiles and found the genes involved were in pathways of cell proliferation, immune response (as would be expected for macrophages) and epigenetic regulation (such as methylation). The observed changes were found not only in the cells treated with talc, but also with the control, the TiO2 beads, although to a lesser degree.[258] Nowhere in this study did the authors identify evidence of gene mutation or carcinogenesis, and the cells studies were not ovarian cells. When confronted with the actual findings of the study, and asked if

[253] Buz'Zard AR., et al. Pycnogenol reduces talc-induced neoplastic transformation in human ovarian cell cultures. *Phytotherapy Research*. 2007; 21(6):579-86.
[254] Shukla A., et al. Alterations in gene expression in human mesothelial cells correlate with mineral pathogenicity. *American Journal of Respiratory Cell and Molecular Biology*. 2009; 41(1):114-23.
[255] Shukla A., et al. Alterations in gene expression in human mesothelial cells correlate with mineral pathogenicity. *American Journal of Respiratory Cell and Molecular Biology*. 2009; 41(1):114-23.
[256] Amended Rule 26 Expert Report of Daniel Clarke-Pearson, MD, dated Nov. 15, 2023, p.18.
[257] Amended Rule 26 Expert Report of Judith Wolf, MD dated Nov. 15, 2023, p. 21.
[258] Emi T et al. Transcriptomic and epigenomic effects of insoluble particles on J774 macrophages. (2021). *Epigenetics*, 16(10), 1053-1070.

Emi et al. (2021) says anything about carcinogenesis, Dr. Clarke-Pearson concedes and contradicts his report stating, "Not that I recall."[259]

Perhaps the most controversial research purporting to demonstrate the biologic plausibility that talc causes ovarian cancer, is that which has been performed by Dr. Ghassan Saed. Dr. Saed's research group has proposed that they have demonstrated the molecular basis of talc increasing the risk of ovarian cancer by demonstrating that ovarian epithelial cells and ovarian cancer cells in culture produce increased levels of CA 125 and ROS, and alter rates of cell proliferation and apoptosis when treated with high doses of talc.[260,261,262] This is not evidence of malignant transformation. Many things elevate the CA 125 level – pregnancy, fibroids, menstrual cycles. CA 125 is not a marker of risk for developing ovarian cancer; nor is it used to make a diagnosis and it is not used to determine the cause of ovarian cancer. CA 125 is a protein that is ubiquitous on epithelial cells and the cells shedding this antigen and the production of ROS in response to the stress of being treated with talc does not mean that it is carcinogenic. Production of ROS is a normal cellular function. Already discussed above is the fact that alterations in the production of ROS and the changes in cell viability are not evidence of malignant transformation or carcinogenesis.

Plaintiffs' experts Drs. Clarke-Pearson and Wolf also rely on Dr. Saed's research in opining that talc can induce specific genetic mutations and malignant transformation in ovarian cells as reported in a 2019 article and two posters presented by his group in 2020 and 2021.[263,264,265,266,267] However, as Dr. Clarke-Pearson acknowledged in his testimony, the mutations reported by Dr. Saed's group have not been associated with ovarian cancer.[268] Further, Dr. Clarke-Pearson acknowledged in his deposition that the mutations that can cause ovarian cancer generally have not been identified.[269] Both of

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[259] January 17, 2024 Deposition Transcript of Daniel Clarke-Pearson, MD, p. 125:19-22.
[260] Fletcher NM., et al. Talcum powder enhances oxidative stress in ovarian cancer cells. *Reproductive Sciences*. 2018; 25:214A-215A.
[261] Fletcher NM., et al. *LB-044 - Talcum Powder Enhances Cancer Antigen 125 Levels in Ovarian Cancer Cells and in Normal Ovarian Epithelial Cells*. Presented at: Society for Reproductive Investigation 65th Annual Scientific Meeting; 2018 March 6-8; San Diego, CA.
[262] Fletcher NM., et al. Molecular basis supporting the association of talcum powder use with increased risk of ovarian cancer. *Reproductive Sciences*. 2019; 26(12):1603-12.
[263] Fletcher NM., et al. Molecular basis supporting the association of talcum powder use with increased risk of ovarian cancer. *Reproductive Sciences*. 2019; 26(12):1603-12..
[264]August 26, 2021 Deposition Transcript of Daniel Clarke-Pearson, MD, pp. 102 & 251.
[265] September 13, 2021 Deposition Transcript of Judith Wolf, MD, pp. 55.
[266] Harper AK, et al. 297 – Poster Session: Talcum powder induces malignant transformation of human primary normal ovarian epithelial cells but not human primary normal peritoneal fibroblasts. *Gynecologic Oncology*. 2020 Oct 1;159:140.
[267] Saed G., et al. *Talcum powder induces a malignant transformation in normal ovarian epithelial cells*. Poster presentation: Department of Obstetrics and Gynecology, Wayne State University and Karmanos Cancer Institute; 2021; Detroit, MI.
[268] August 26, 2021 Deposition Transcript of Daniel Clarke-Pearson, MD, pp. 102 & 106.
[269]August 26, 2021 Deposition Transcript of Daniel Clarke-Pearson, MD, p. 290.

Dr. Saed's posters provide very little information from which to evaluate his studies. In the first study from 2020, he reports that treatment with talc of "[h]uman primary normal ovarian epithelial cells" leads to malignant transformation as these cells exhibit anchorage-independent growth. His conclusion, however, is erroneous as anchorage-independent growth is only a phenotype and many different cells can display this type of growth without being cancerous. In fact, it is commonplace for cells that have been transformed to grow in colonies, which the cells he used in his experiments may very well be, we just do not know, as he has not provided the reader with any of that data. Without actually sequencing the DNA from these cells, no conclusions can be drawn as to whether or not they are actually malignant. In the second poster from 2021, the limited data provided simply shows that he stained cells for p53 and Ki67 before and after treatment with talc. He claims in the poster that he saw more p53 and Ki67 in the cells post talc treatment, but since he didn't actually sequence the DNA, he has not proven that the DNA has been mutated.

Dr. Saed combined the experiments he presented in the above two posters into one manuscript. He submitted this manuscript for consideration of publication to no less than *five* journals whose publication focus tends to be on cancer biology, gynecologic oncology and basic science. He was told by the editors of all five of these journals that his work was not acceptable for publication. Comments from the reviewers for the journals echoed my comments and concerns, stating that "the author's conclusions suggesting acute exposure of talc powder to ovary epithelial cells is associated with ovarian cancer are outrageous and not supported by the manuscript's data"[270] and "[t]he problems with this submission are too numerous to count, and the science, methodology, and data cannot be trusted."[271] If Dr. Saed's work was truly demonstrating malignant transformation, as he and plaintiffs' experts claim, this work would be noteworthy and accepted at reputable journals with high impact value, and it is not. Instead, his work was summarily rejected with comments from the reviewers such as "these data are too premature for publication"[272] and instructions from the editors to Dr. Saed "that a revised version of the current manuscript should not be submitted for another review to *Gynecologic Oncology*."[273] Ultimately, Dr. Saed's manuscript was accepted for publication in an obscure journal titled *Minerva Obstetrics and Gynecology* with an impact value of 1.4 and a subject focus of general obstetrics and gynecology, not cancer biology.[274] With the publication of the full manuscript, the methodology of the experiments conducted by Dr. Saed are now available for review. Dr. Saed's claim that he has now demonstrated the mechanism by which talc induces malignant transformation in ovarian cells, akin to a woman's genital application of perineal talc, is unfounded. Dr. Saed analyzed cells with a one-time application of talc

[270] SAED_SEPT222021_SUPPL_000101
[271] SAED_SEPT222021_SUPPL_000104
[272] SAED_SEPT222021_SUPPL_000070
[273] SAED_SEPT222021_SUPPL_000069
[274] Harper, AK, et al. Talcum powder induces malignant transformation in normal human primary ovarian epithelial cells. *Minerva Obstetrics and Gynecol*. 2023 Apr;75(2):150-157.

and then looked at colony growth and staining for p53 and Ki67. None of these measures actually analyzed the DNA to determine if there were mutational changes, which is the only analysis that can definitively identify malignant transformation. Additionally, talc was applied to the cells in culture only once, which does not correlate with the chronic perineal application of genital talc in women. There is also no rationale to the doses of talc that he applied to the cells except for the fact that he states he has used them before and even he admits "[t]hese doses are not intended to represent a typical dose applied to the genital area in women over time."[275] Then what exactly is the point of these experiments? Additionally, Dr. Saed states that he used normal peritoneal fibroblasts as control cells for these experiments and reports that he did not see colony growth or increases in staining for p53 and Ki67 in these cells as he did in the ovarian cells, when they were treated with talc. Careful review of his data, however, demonstrates that the fibroblasts actually decreased their proliferation rate to below control levels, with treatment of these cells with talc or titanium oxide beads, meaning that there are no controls in these experiments at all (see Figure 2 of Harper (2023)).[276] Notably, at the conclusion of the article, the authors state "[a] portion of Ghassan M. Saed's time conducting this research was paid for by the lawyers representing plaintiffs in the talcum powder litigation."[277] In other words, not only has Dr. Saed served as an expert witness for plaintiffs, but the research itself was at least partially funded by plaintiffs' attorneys.

Setting aside the numerous methodological and potentially ethical shortcomings of Dr. Saed's work, he does not answer the question whether talc can cause mutations that are actually responsible for the initiation or promotion of ovarian cancer. As acknowledged by plaintiffs' expert Dr. Judith Wolf at her deposition, the different subtypes of ovarian cancer have different etiologies,[278] making it unlikely that a single type of exposure could be responsible for a broad enough range of genetic mutations to cause several distinct subtypes of ovarian cancer (but no other gynecological cancers).

With respect to *in vivo* animal studies examining the risk of developing ovarian cancer with exposure to talc, the study by Hamilton (1984) is perhaps the best designed to answer this question.[279] The authors of this study performed intrabursal injections of rat ovaries with talc and then sacrificed the rats at variable time points (1, 3, 6, 12, and 18 months) for post-mortem analysis (fifty rats in total). Appropriate controls included rats with sham operations and sham-treated rats. None of the rats in the experimental,

[275]Harper AK, et al. Talcum powder induces malignant transformation in normal human primary ovarian epithelial cells. *Minerva Obstetrics and Gynecol.* 2023 Apr;75(2):150-157.
[276] Harper AK, et al. Talcum powder induces malignant transformation in normal human primary ovarian epithelial cells. *Minerva Obstetrics and Gynecol.* 2023 Apr;75(2):150-157.
[277] Harper AK, et al. Talcum powder induces malignant transformation in normal human primary ovarian epithelial cells. *Minerva Obstetrics and Gynecol.* 2023 Apr;75(2):150-157
[278] September 14, 2021 Deposition Transcript of Judith Wolf, MD, pp. 569-570.
[279] Hamilton TC., et al. Effects of talc on the rat ovary. *British Journal of Experimental Pathology*. 1984; 65(1):101.

talc-injected group developed ovarian cancer, or any evidence of pre-cancer and the ovarian tissue did not have atypia or evidence of mitosis. Importantly, there was evidence of foreign-body granuloma formation in the ovaries, but again, no evidence of neoplasia or precancer. Four of the experimental rats were noted to have papillary formations on the surface of the ovarian tissue, but there was no atypia associated with these lesions. These papillary lesions were also noted to be without evidence of an association with the foreign body granulomas and therefore were thought not to be a reaction to an inflammatory process. Rather, the authors hypothesized that since the talc blocked the normal drainage channels of the ovary and caused cysts to form in the bursa, the papillary formations resulted from the long-term high concentration of steroid hormones in the entrapped follicular fluid.[280]

Summary

In vitro studies on the biologic effects of talc on ovarian epithelial cells have been limited and generally have examined patterns of gene expression, changes in proliferation and cell viability. Oxidative stress, production of reactive oxygen species and increased cell proliferation are all normal cellular functions. None of these endpoints is definitively tied to malignant transformation, and as a result, they cannot be extrapolated as providing evidence of an association between talc and an increased risk of developing ovarian cancer. This is especially true when the results of these studies conflict with each other, as is the case with Buz'Zard and Shukla.[281,282] With respect to animal studies, as is the case for the *in vitro* studies, none of these studies has ever demonstrated malignant transformation, and there is simply no evidence that talc can induce a process of malignant transformation in ovarian epithelial cells.[283] In order to have biologic plausibility, there has to be *some* data to support the hypothesis. In the practice of medicine, we must be guided by actual science, not just guessing games. The science does not support the proposition that the perineal application of talc increases the risk of developing ovarian cancer.

Talc as the Vehicle by which Other Substances Can Cause Ovarian Cancer

Plaintiff's experts also hypothesize that cosmetic talcum powder is either contaminated by certain substances or has been mixed with substances that are the actual cancer-causing agents. The substance that has received the most attention in this arena is asbestos. In 2012, IARC (the International Agency for Research on Cancer) released a monograph on asbestos in which the Working Group noted a causal association

[280] Hamilton TC., et al. Effects of talc on the rat ovary. *British Journal of Experimental Pathology*. 1984; 65(1):101.
[281] Buz'Zard AR., et al. Pycnogenol reduces talc-induced neoplastic transformation in human ovarian cell cultures. *Phytotherapy Research*. 2007; 21(6):579-86.
[282] Shukla A., et al. Alterations in gene expression in human mesothelial cells correlate with mineral pathogenicity. *American Journal of Respiratory Cell and Molecular Biology*. 2009; 41(1):114-23.
[283] Hamilton TC., et al. Effects of talc on the rat ovary. *British Journal of Experimental Pathology*. 1984; 65(1):101.

between heavy occupational exposure to asbestos and cancer of the ovary.[284] IARC classifies asbestos as a Group 1 agent, meaning that it is carcinogenic to humans, but notably, the perineal application of talc is in Group 2b, meaning that there is only limited evidence of carcinogenic potential in humans and so it is listed only as *possibly* carcinogenic, along with other 2b substances such as aloe vera and pickled vegetables.[285] This classification, which was issued in 2010, seems suspect and somewhat outdated as it was based only on studies published through 2006, which consisted mainly of the case-control literature, and without the benefit of the prospective cohort studies (Gates 2010, Houghton 2014, Gonzalez 2016 and O'Brien 2020) which are much less subject to the biases inherent in the case-control studies.[286,287,288,289]

The IARC working group conceded in the asbestos monograph that there was a paucity of data to examine. Its conclusions were based upon five published studies that showed a statistically significant association from heavy occupational exposure.[290,291, 292,293, 294] IARC also considered studies on women that involved environmental exposure, but these studies did not show a statistically significant increased risk.[295] There are several problems with the conclusion that IARC has drawn. First is the problem of misclassification. The studies that were published used data from death certificates, not prospective medical records or an examination of the actual tumors. It is quite possible that the subjects in the studies cited in the monograph actually had peritoneal mesothelioma (a disease known to be caused by asbestos), not ovarian cancer, as these two diseases have historically been difficult to distinguish clinically. From a pathologic standpoint, the distinction can be made by examining the individual tumor immune

[284] International Agency for Research on Cancer. IARC monographs on the evaluation of carcinogenic risks to humans, Vol 100C. Arsenic, Metals, Fibres and Dusts. *Lyon: World Health Organization*, 2012.
[285] International Agency for Research on Cancer. IARC monographs on the evaluation of carcinogenic risks to humans, Vol 93. Carbon Black, Titanium Dioxide, and Talc. *Lyon: World Health Organization*, 2010.
[286] Gates MA., et al. Risk factors for epithelial ovarian cancer by histologic subtype. *American Journal of Epidemiology*. 2010; 171:45-53.
[287] Houghton SC., et al. Perineal powder use and risk of ovarian cancer. *Journal of the National Cancer Institute*. 2014; 106(9):208.
[288] Gonzalez N., et al. Douching, talc use, and risk of ovarian cancer. *Epidemiology*. 2016; 27(6):797-802.
[289] O'Brien, KM, et al. Association of powder use in the genital area with risk of ovarian cancer. *JAMA*. 2020; 323(1), 49-59.
[290] Acheson ED., et al. Mortality of two groups of women who manufactured gas masks from chrysotile and crocidolite asbestos: a 40-year follow-up. *British Journal of Industrial Medicine* 1982; 39:344–8.
[291] Berry G., et al. Mortality from all cancers of asbestos factory workers in East London 1933-80. *Occupational and Environmental Medicine* 2000; 57:782-5.
[292] Germani D., et al. Cohort mortality study of women compensation for asbestosis in Italy. *American Journal of Industrial Medicine* 1999; 36129-34.
[293] Langseth H., et al. Asbestos fibers in ovarian tissue from Norwegian pulp and paper workers. *International Journal of Gynecological Cancer*. 2007; 17(1):44-9.
[294] Magnani C., et al. Cancer risk after cessation of asbestos exposure: a cohort study of Italian asbestos cement workers. *Occupational and Environmental Medicine* 2008; 5:164-70
[295] International Agency for Research on Cancer. IARC monographs on the evaluation of carcinogenic risks to humans, Vol 100C. Arsenic, Metals, Fibres and *Dusts*. *Lyon: World Health Organization*, 2012.

profiles and by systematically examining immunohistochemistry markers.[296] Much of this technology was not available in the 1980s and 1990s, when three of the five studies cited by IARC were published. Additionally, none of the studies cited in the IARC monograph controlled for other risk factors known to be associated with ovarian cancer development. The importance of controlling for well-established risk factors known to be associated with the risk of developing ovarian cancer is borne out by a recent study published by Vidican (2022).[297] The authors of this study stratified exposure to asbestos as either direct or indirect and looked at 3 levels of exposure and the risk of developing various histologic subtypes of ovarian cancer. They reported statistically significant findings only for the group with indirect exposure of a moderate level. However, when they adjusted their findings based on a familial history of ovarian cancer – a factor known to increase the risk of developing ovarian cancer by 3-5-fold, no significant associations between asbestos exposure and high-grade serous carcinoma were found. Again, the conclusions drawn by IARC have to be evaluated in the context of what is known about ovarian cancer in its totality now, and not in isolation of some studies that were conducted decades ago, prior to the current state of the science.

These criticisms of the conclusions published by the IARC Working Group regarding asbestos and the development of ovarian cancer are not made by me in isolation. Recently, Dr. Slomovitz and four other distinguished professors of gynecologic oncology called into question the same "historical" evidence and concluded that "it is weak and inconsistent."[298] The authors explained that the finding in the IARC review of an excess of ovarian cancer cases is more likely due to a misclassification of peritoneal malignant mesothelioma cases misdiagnosed as ovarian cancer cases and that "[w]ithout an expert pathologic review, it is extremely difficult to establish – as the IARC Working Group has intimated – a clear 'causal association' between ovarian cancer and heavy occupational exposure to asbestos."

Plaintiffs frequently cite to the meta-analysis published by Camargo (2011) as additional data that asbestos can cause ovarian cancer.[299] Camargo reported a statistically significant standardized mortality ratio (SMR) of 1.77 (1.37,2.28) for the association between asbestos and ovarian cancer. This analysis, however, is suspect given the issue of misclassification. Since all but one of the studies in the meta-analysis relied upon death certificates and reported on SMR instead of pathology reports and standardized incidence ratios (SIR), we do not know how many of these subjects actually had

[296] Taşkın S., et al. Malignant peritoneal mesothelioma presented as peritoneal adenocarcinoma or primary ovarian cancer: Case series and review of the clinical and immunohistochemical features. *International Journal of Clinical and Experimental Pathology*. 2012; 5(5):472-8.
[297] Vidican P., et al. Frequency of Asbestos Exposure and Histological Subtype of Ovarian Carcinoma. *International Journal of Environmental Research and Public Health*, 2022; 19(9):5383.
[298] Slomovitz B., et al. Asbestos and ovarian cancer: examining the historical evidence. *International Journal of Gynecologic Cancer* 2021; 31(1).
[299] Camargo MC., et al. Occupational exposure to asbestos and ovarian cancer: a meta-analysis. *Environmental Health Perspectives*. 2011; 119(9):1211-7.

peritoneal mesothelioma and not ovarian cancer. In fact, the authors noted that they found higher effect estimates for subjects that had been diagnosed with asbestosis, thereby demonstrating a potential bias and increasing the likelihood that many of these cases were misclassified. The authors also reported a moderate degree of heterogeneity among the studies included in the meta-analysis, indicating that they are all quite discordant and the "meaningfulness" of analyzing these studies as a group is quite limited.

Interestingly, Reid al. published a separate review and meta-analysis in 2011, also addressing whether or not asbestos is a risk factor for the development of ovarian cancer.[300] In contrast to Camargo, Reid's meta-analysis relied on diagnoses of confirmed cases of ovarian cancer, not on SMR, and did not find a statistically significant association between asbestos exposure and the diagnosis of ovarian cancer, reporting an effect size of 1.29 (CI 0.97,1.73). The authors conclude that the increased rates reported in prior analysis, compared with reference populations were likely from disease misclassification.

Langseth (2007) examined the ovaries of women who worked in the paper and pulp industry, employment known to be associated with occupational exposure to asbestos.[301] The authors identified 31 cases of ovarian cancer for which tissue was available and compared them to 86 control subjects (41 with cancer and no exposure and 45 with no cancer and no exposure). Only two of the cases were found to have asbestos in their ovaries, and one of these women was not actually working with asbestos, meaning that she possibly had second-hand exposure. None of the control subjects had asbestos in her ovaries. The authors conclude that asbestos does not contribute as a causal factor in the development of ovarian cancer in either women with occupational exposure to asbestos or in the general public.

Recently, Dasgaard (2022) and colleagues published a comprehensive study examining the risk of multiple cancers after environmental exposure to asbestos in childhood.[302] This was a long-term prospective cohort study that enrolled 12,111 former school-aged children who lived within a distance of 100-750m downstream from a large asbestos-cement plant. They then calculated standardized incidence ratios (SIR) for asbestos-related cancers, all cancers and multiple cancers. The SIR for the school cohort was modestly increased at 1.07 (CI 1.02,1.12) with the increase primarily being driven by an increased risk of malignant mesothelioma which was found to have an SIR 8.77 (CI 6.38-12.05). Importantly, the risk of developing ovarian cancer was actually shown to be

[300] Reid A., et al. Does exposure to asbestos cause ovarian cancer? A systematic literature review and meta-analysis. Cancer *Epidemiology and Prevention Biomarkers* 2011; 20(7), 1287-1295.
[301] Langseth H., et al. Asbestos fibers in ovarian tissue from Norwegian pulp and paper workers. *International Journal of Gynecological Cancer*. 2007; 17(1):44-9.
[302] Dalsgaard, SB., et al. Cancer incidence and risk of multiple cancers after environmental asbestos exposure in childhood - A long-term register-based cohort study. *International Journal of Environmental Research and Public Health*. 2022; 19(1):268.

decreased, with an SIR 0.71 (CI 0.50-0.99). Although this finding was statistically significant, no one would advocate asbestos exposure as a methodology to decrease the risk of developing ovarian cancer, however, it is an important finding as it is the largest study to look specifically at incidence rates in a population that was verifiably exposed under both environmental and occupational conditions. Importantly, this data was not available when IARC published the 2012 monograph.

Asbestos is ubiquitous in the environment, as asbestos fibers can be found in the ovaries of women with documented household exposure as well as in women with no reported history of asbestos exposure.[303] This does not necessarily mean, however, that the asbestos migrated retrograde from the perineum through the genital tract to the ovaries. The path of migration has not been established in either men or women. Autopsies on patients with a large number of asbestos fibers in their lungs also found asbestos fibers in nine different organs, meaning that they could have passed into the blood or lymphatic system and were deposited at different sites.[304] Regardless of how the asbestos migrated to the ovaries, the balance of the evidence does not support a causal role for asbestos in the development of ovarian cancer.

In any event, if talc is the vehicle by which the proposed carcinogen (e.g., asbestos) is being delivered to the ovaries, then the epidemiologic literature on perineal application of talc and the development of ovarian cancer should be consistent and scientifically credible. And it is not. My opinion does not change regardless of the composition of the talcum powder because the published, peer-reviewed literature does not support an increased risk of developing ovarian cancer with perineal application of talc.

Health Canada Screening Assessment on Talc

In April 2021, Health Canada published its screening assessment of the risk of ovarian cancer with the perineal application of talc,[305] concluding that the perineal application of talc supports a modest association with an increased risk of ovarian cancer. Health Canada reached its conclusions based on a flawed application of a Bradford Hill analysis. First, Health Canada relies upon and cites expert reports from litigation matters – these reports are not peer reviewed and are not considered objective scientific research. Second, Health Canada states that the published literature is consistent, which as outlined above, it is not. Health Canada does concede that information on biologic gradient, which would establish dose-response, is lacking and there is no evidence of a linear, non-linear or even threshold dose. As for biologic plausibility, Health Canada states that "[a]lthough a specific order of events by which perineal talc exposure could

[303] Heller DS., et al. Asbestos exposure and ovarian fiber burden. *American Journal of Industrial Medicine*. 1996; 29:435-9.
[304] Langseth H., et al. Asbestos fibers in ovarian tissue from Norwegian pulp and paper workers. *International Journal of Gynecological Cancer*. 2007; 17(1):44-9.
[305] Health Canada, Screening Assessment Talc (April 2021).

lead to ovarian cancer has not been established, several recent publications…support the hypothesis that perineal talc exposure leading to ovarian cancer is biologically plausible."[306] It is notable that the five studies cited in support of the preceding statement all have paid plaintiff experts as co-authors.[307,308,309, 310,311] For all the reasons already discussed in this report, any claim of biological plausibility is speculative. In short, the Health Canada assessment essentially regurgitates the opinions of plaintiffs' experts in talc litigation and does not add anything new to the body of science.

Conclusions

As a physician who has dedicated her career to the care of women who develop ovarian cancer, I hope that someday we will know what causes ovarian cancer. There are risk factors that are well established and consistently supported by the scientific literature and by the observations made in the clinical practice of medicine. These include age, genetic predisposition, family and personal history of cancer, reproductive factors, endometriosis and postmenopausal hormone replacement therapy. These are the same risk factors that are recognized by the national organizations that investigate and research the causes of ovarian cancer and include the SGO, AGOG, CDC and NCI. Knowing more about the cause of this deadly disease would allow us to take more effective measures to help reduce its incidence and mortality rate. This is in part what we have done by performing risk-reducing surgery on women who carry genetic mutations that predispose them to the development of the disease, which accounts for ~ 20-25% of ovarian cancer cases. After thorough review and consideration of all of the available data, it is my opinion that the perineal application of talc is not a risk factor for the development of ovarian cancer. As explained in this report, purported associations are weak, the epidemiologic literature is highly inconsistent, and theories with respect to migration and the mechanism by which talc might cause cancer through inflammation are nothing more than speculation, unsupported by any actual science. Attributing a causal role to talc in the development of ovarian cancer will not save any lives or otherwise help women because the incidence and mortality of the disease will not be reduced by false science. Physicians have an obligation to practice evidence-based medicine in a manner that will most benefit our patients and not engage in speculation that is not borne out by data.

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[306] Health Canada, Screening Assessment Talc (April 2021).

[307] Campion A., et al. Identification of foreign particles in human tissues using Raman microscopy. *Analytical Chemistry*. 2018; 90(14):8362-9.

[308] Fletcher NM., et al. Molecular basis supporting the association of talcum powder use with increased risk of ovarian cancer. *Reproductive Sciences*. 2019; 26(12):1603-12.

[309]Mandarino A., et al. The effect of talc particles on phagocytes in co-culture with ovarian cancer cells. *Environmental Research*. 2020; 180:108676.

[310] McDonald SA., et al. Migration of talc from the perineum to multiple pelvic organ sites: five case studies with correlative light and scanning electron microscopy. *American Journal of Clinical Pathology*. 2019; 152(5):590-607.

[311] McDonald SA., et al. Correlative polarizing light and scanning electron microscopy for the assessment of talc in pelvic region lymph nodes. *Ultrastructural Pathology*. 2019; 43(1):13-27.

Exhibit A

November 2023

UNIVERSITY of CALIFORNIA, SAN DIEGO
MEDICAL CENTER MOORES CANCER CENTER

CURRICULUM VITAE

PERSONAL

NAME:	Cheryl Christine Saenz, M.D.
MAIDEN NAME:	Cheryl Christine Gurin, M.D.
POSITION:	Clinical Professor University of California, San Diego School of Medicine
BUSINESS ADDRESS:	Moores UCSD Cancer Center Division of Gynecologic Oncology 3855 Health Sciences Drive Mail Code: 0987 La Jolla, CA 92093-0987 Academic Office: (858) 822-6275 Case Manager: (858) 822-5417 Fax: (858) 822-6319 Email: csaenz@ucsd.edu
DATE OF BIRTH	August 1961

EDUCATION

COLLEGE:	Cornell University College of Arts and Sciences Ithaca, NY B.A. 1985 Biopsychology
MEDICAL SCHOOL:	University of California, Irvine College of Medicine Irvine, CA M.D. 1991

POSTDOCTORAL TRAINING

Resident in Reproductive Medicine
University of California Medical Center
San Diego, CA
1991-1995

Galloway Fellow
Memorial Sloan-Kettering Cancer Center
New York, NY
1993

Fellow in Gynecologic Oncology
Memorial Sloan-Kettering Cancer Center
New York, NY
1995-1998

Junior Faculty Mentoring Fellowship
National Center for Leadership in Academic Medicine
University of California, San Diego
San Diego, CA
2001

Women's Reproductive Health Research Scholars Program
Principal Investigator: Thomas R. Moore, M.D.
Mentor: Steven F. Dowdy, Ph.D.
Departments of Reproductive Medicine and Cellular and Molecular Medicine
University of California, San Diego
Agency: NIH HD-99-001
Research Career Development Center in Reproductive Sciences
Fellow, September 2002 – February 2007

Physician Leadership Academy
University of California, San Diego
San Diego, CA
2007 – 2009

Mid-Career Women Faculty
Professional Development Seminar
Association of American Medical Colleges/Harvard Medical School
Scottsdale, AZ
December 2008

CERTIFICATION

American Board of Obstetrics and Gynecology – 1999
Recertification 2022
Subspecialty of Gynecologic Oncology – 2001
Recertification 2022
Certificate #: 950475

LICENSING

California - GO74647 (1992)
New York - 199704 (Inactive)
U.S. Drug Enforcement Administration - BG3305100

ACADEMIC APPOINTMENTS

Assistant Clinical Professor
Division of Gynecologic Oncology
Department of Reproductive Medicine
University of California, San Diego School of Medicine
October 1998 – June 2004

Associate Clinical Professor
Division of Gynecologic Oncology
Department of Reproductive Medicine
University of California, San Diego School of Medicine
July 2004 – June 2010

Clinical Professor
Division of Gynecologic Oncology
Department of Reproductive Medicine
University of California, San Diego School of Medicine
July 2010 – Present

ADMINISTRATIVE APPOINTMENTS

Interim Director, Infusion Center
Moores Cancer Center
UC San Diego Health System
2006–2007

Leader, Internal Task Force
Comprehensive Patient Safety Audit
Moores UCSD Cancer Center Infusion Center
April 2007

Director for Ambulatory Access
UCSD Medical Group
University of California, San Diego School of Medicine
August 2007 – July 2012

Medical Director
Strauss Family Center for the Early Detection of Ovarian Cancer
July 2010 - Present

SCIENTIFIC AND MEDICAL SOCIETIES

1995 – Present	Fellow American Congress of Obstetrics and Gynecology
1999 - Present	Diplomat American Board of Obstetrics and Gynecology
1998 - Present	Full Member Society of Gynecologic Oncology
2001 – Present	Fellow American College of Surgeons
2001 - Present	Full Member Western Association of Gynecologic Oncologists
2006 – Present	Full Member American Association for Cancer Research
2006 – Present	Full Member American Society of Clinical Oncology

SCHOOL OF HEALTH SCIENCES COMMITTEES

1999 – 2012	Member, Cancer Committee University of California, San Diego Medical Center
2001 – 2012	Chair, Cancer Committee University of California, San Diego Medical Center
2001 – 2012	Member, Quality Council University of California, San Diego Medical Center
2002 – 2016	Co-Leader, Gynecologic Oncology Specialized Cancer Units Moores UCSD Cancer Center

2005 – 2009	Member, Service Excellence Committee Moores UCSD Cancer Center
2006 – 2008	Subcommittee Leader, Programs of Excellence Strategic Planning Committee Moores UCSD Cancer Center
2007 – 2012	Member, Board of Governors University of California, San Diego Medical Center
2007 – 2012	Member, Cancer Center Cabinet Moores UCSD Cancer Center
2007 – 2012	Member, Medical Group Operations Committee University of California, San Diego Medical Group
2007 – 2012	Member, Professional Standards Committee University of California, San Diego Medical Group
2007 – 2016	Women's Reproductive Health Research Scholars Program Member, Internal Advisory Board
2007 – Present	Member, Academy of Clinical Scholars UCSD School of Health Sciences
2010 – 2012	Member, Dean's Executive Council Faculty Development Committee UCSD School of Health Sciences
2011 – 2012	Chair, Professional Standards Committee University of California, Medical Group
2013	Member, Five-year Review Committee for Reappointment of Chair of the Department of Anesthesiology
2014 – 2017	Member-At-Large Health Sciences Faculty Council
2014 – 2020	Member Health Sciences Faculty Equity Committee
2020 – Present	Member, Quality and Value Committee Moores UCSD Cancer Center

2020 – Present	Member, Surgery Quality Committee UC San Diego Health Systems

PROFESSIONAL SOCIETY COMMITTEE APPOINTMENTS

Member, Coding Taskforce
Society of Gynecologic Oncology
2019-2020

Member, Media Response Team
Foundation for Women's Cancer
2002-2016

Member, Marketing and Communications Committee
Society of Gynecologic Oncology
2004-2013

Board of Directors
Foundation for Women's Cancer
2007 – 2013

Member, Cervix and Vulvar Cancer Committee
Gynecologic Oncology Group
2009-2012

Co-Chair, Education Committee
Foundation for Women's Cancer
2009-2012

Member, 2010 Program Committee
Western Association of Gynecologic Oncologists
Annual Meeting on Gynecologic Cancers
2009-2010

Chair, Media Relations Subcommittee
Marketing and Communications Committee
Society of Gynecologic Oncology
2010-2012

Member, 2011 Program Committee
Society of Gynecologic Oncology
Annual Meeting on Women's Cancer
2010-2011

Chair, Education Committee
Foundation for Women's Cancer
2012-2016

Member, Society of Gynecologic Oncology
2013 Nominating Committee

AD HOC REVIEWER

Gynecologic Oncology
American Journal of Obstetrics and Gynecology
Cancer
Obstetrics and Gynecology
Journal of Pediatric Surgery Case Reports

HONORS AND ACTIVITIES

Content Expert, Analysis of Assembly Bill 547
Ovarian Cancer Screening
California Health Benefits Review Program
A Report to the 2003-2004 California Legislature

Course Director, Ovarian Cancer Survivors' Course
Moores UCSD Cancer Center/Gynecologic Cancer Foundation
January 2006

Walter T. Danreuther Award
The American Association of Obstetricians and Gynecologists Foundation
September 2006

Content Expert, Analysis of Assembly Bill 1774
Coverage for Gynecologic Cancer Screening Tests
California Health Benefits Review Program
A Report to the 2007-2008 California Legislature

Course Director, Cancer Biology
Young Women in Cancer Research Oncofertility Academy
Better Education for Women in Science and Engineering Program
2008-2016

Course Director, Gynecologic Cancer Wellness Symposium
'From Tai Chi to Chai Tea – What You Can Do to Promote Gynecologic Health', Supported by the Web MD Foundation and the Gynecologic Cancer Foundation, Moores UCSD Cancer Center
January 2010

Expert Reviewer, Gynecologic Oncology
Medical Board of California, Department of Consumer Affairs
January 2021 - Present

HOSPITAL APPOINTMENTS

Attending Surgeon
UC San Diego Health System– San Diego, CA
10/98 – Present

Attending Physician
Scripps Memorial Hospital – San Diego, CA
1/99 – 2011

Attending Physician
Rady Children's Hospital - San Diego, CA
10/99 - 2012

Attending Physician
Palomar/Pomerado Health Care System
11/99 - 2010

SELECTED LECTURESHIPS AND PRESENTATIONS

"Ten-year Trends in Pre-invasive and Invasive Cervical Neoplasia in Southern California", Western Association of Gynecologic Oncologists, 1995.

"Pathological Risk Factors and Outcomes for Isolated Adnexal Metastases in Endometrial Cancer", Society of Memorial Gynecologic Oncologists, 1996.

"Clinicopathologic Features of Endometrial Cancer Occurring in Patients with a Family History Suspicious for Hereditary Nonpolyposis Colorectal Cancer", Society of Gynecologic Oncologists, 1998.

"Fertility Agents and the Risk of Ovarian Cancer", Grand Rounds, Department of Reproductive Medicine, University of California, San Diego, 1999.

"The Use of Operative Laparoscopy in Gynecologic Oncology", A Gynecologic Oncology Update Seminar, San Diego, CA, 1999.

"Fertility Agents and the Risk of Ovarian Cancer", San Diego Gynecologic Society, San Diego, CA, 1999.

"Ovarian Cancer" Lecture Hematology/Oncology Fellows, Veterans Administrative Hospital, San Diego, CA, 2000.

"Gynecologic Cancer Screening in the Year 2000", UCSD Cancer Center Associates Meeting, San Diego, CA, 2000.

"Abnormal Pap Smears", Advances in Urology and Gynecology for Primary Care Seminar, San Diego, CA, 2000.

"Advances in Gynecologic Cancer Treatment", The Wellness Community, San Diego, CA, 2000.

"Gynecologic Oncology Cancer Survivorship", Cancer Survivorship Seminar, San Diego, CA, 2000.

"Screening Your Patient Over 40 for Gynecologic Malignancies", Current Trends in Women's Health Seminar, San Diego, CA, 2000.

"Abnormal Pap Smears", Advances in Urology and Gynecology for Primary Care Seminar, San Diego, CA, 2001.

“Update in Gynecologic Cancers”, Advances in Urology and Gynecology for Primary Care Seminar, San Diego, CA, 2002.

“Treatment of Terminal Peritoneal Carcinomatosis by a Transducible p53-Activating Peptide”, Grand Rounds, Department of Reproductive Medicine, University of California San Diego, 2004.

“Selective Targeting and Killing of Tumor Cells Expressing Tumor-Associated Receptors by Transducible Anti-Cancer Peptides”, Women’s Reproductive Health Research Scholars’ Symposium, Cincinnati, OH 2005.

“HPV and the Abnormal Pap Smear – What We’ve Learned in the Last Five Years”, Primary Care Grand Rounds, Departments of Reproductive Medicine and Family Medicine, University of California San Diego, 2006.

“Selective Targeting and Killing of Tumor Cells Expressing Tumor-Associated Receptors by Transducible Anti-Cancer Peptides”, American Gynecologic Club Annual Meeting, La Jolla, CA, 2006.

“Ovarian Cancer – What You Need to Know”, Faculty Ambassador Event, Moores UCSD Cancer Center, LA Jolla, CA 2007.

“HPV and Cervical Cancer: Current Screening Guidelines”, Sidney Kimmel Cancer Center Seminar, La Jolla, CA, 2008.

"Surgical Management of the Placenta Accreta", 5th Annual Perinatalogy Symposium, Department of Reproductive Medicine, University of California, San Diego, 2008.

"Chemotherapy in Cancer," Young Women in Cancer Research Saturday Academy, Oncofertility Consortium, Moores UCSD Cancer Center, University of California, San Diego, 2008.

"What Can I Do if I'm at Risk for Ovarian Cancer", Management of the High Risk Patient, Ovarian Cancer Community Outreach Symposium, Moores UCSD Cancer Center, La Jolla CA, 2008.

"Family History, Genetic Risk and Ovarian Cancer"
Ovarian Cancer Survivors Courses, Gynecologic Cancer Foundation, San Antonio, Texas, 2009, Phoenix AZ, 2009, Las Vegas, NV, 2009, Richmond VA, 2010, Washington D.C., 2011, Austin TX 2012, Las Vegas, 2013.

"The Hereditary Component of Ovarian Cancer"
Women's Wellness Day
UC San Diego Health System, La Jolla CA, 2013.

"The Hereditary Component of Ovarian Cancer"
Society of Gynecologic Nurse Oncologists
31st Annual Symposium
April 2013, San Diego, CA

"The Invasive Placenta – A Multidisciplinary Team Approach Utilizing Balloon Catheters"
2015 Annual Meeting on Women's Cancer
Postgraduate Course Lecture
March 2015, Chicago, IL

RESEARCH SUPPORT

Current Research Support
1 R43 CA254586-01A1
Agency: NIH/NCI
Project title: "A Novel, Low-Cost, Handheld, 3D Imaging System for Improved Screening of Cervical Neoplasia in Resource Limited Settings"
Period: April 20, 2021 through January 19, 2022
PI: Joe Carson
Co-I: Cheryl C. Saenz
Total funding award: $399,979 Summary of grant activities: This study intends to evaluate the design and engineering of an innovative, minimally invasive, 3D, medical imaging device (CervImage™) for detecting cervical lesions. The

evaluation will be enabled via a 20-patient pilot clinical program at UCSD. The project aims to develop and establish the feasibility of the CervImage™ technology for obtaining clinical 3D photographs and for recording measurable 3D parameters in human cervices, and aims to use the resulting images to determine which design and engineering improvements to the CervImage™ device are required. The results will be compared with those obtained for the same patients through the conventional visual screening examination. The clinical study investigators hypothesize that CervImage ™will substantially improve cervical image quality and resolution as compared to conventional visual screening examination procedures.

Completed Research Support

'Creating an Early Detection Test for Ovarian Cancer"
Principal Investigator: Christian Barrett
Co-Principal Investigator: Cheryl Saenz
Agency: Strauss Center for the Early Detection of Ovarian Cancer
Pilot Project Award
Period January 2014-December 2015
This study seeks to identify ovarian cancer in its earliest stages through the detection of RNA isoforms unique to ovarian cancer cells in cells collected from Pap smears.

"Translational Cancer Genomics: Application of the novel Network-based Stratification Technique to identify clinically relevant prognostic information from tumor somatic mutation profiles"
Principal Investigator: Trey Ideker
Co- Principal Investigators: Cheryl Saenz, Stephen Howell
Agency: UC San Diego Moores Cancer Center Translational and Clinical Pilot Project Award
Period: May 2013-April 2014
This project will utilize a recently developed novel way of analyzing the information gained from genomic analyses of ovarian cancers that allows us to 'cluster' the mutations found in a manner that can predict response to chemotherapy as well as prognosis. As the cost of sequencing whole genomes or exomes remains quite high, in order to make this analysis more clinically useful, we seek to identify smaller sets of these 'predictive mutations' that could be then used cost effectively in the clinics to guide treatment options and decisions.

1R21CA162718-01
National Institutes of Health (NCI) $500,000
PI: Loren Mell
Co-PI: Cheryl C. Saenz
Period: October 2011-September 2014
Image-guided bone marrow-sparing IMRT for cervical cancer
Major Goals: To estimate rates of acute hematologic toxicity associated with image-guided functional bone marrow-sparing intensity modulated radiation therapy in an international dual-center clinical trial

Clinical Investigator Team Leadership Award
Supplement to Specialized Cancer Center Support Grant
Agency: NCI 5P30CA23100-26
Period September 2010-August 2012
The support provided by this award is intended to allow the investigator to expand leadership responsibilities in investigator-initiated and Cooperative Group trials, increase accrual to clinical trials and continue to develop relationships with basic science researchers that allow for the bridging between basic science and clinical studies.

Women's Reproductive Health Research Scholars Program
Principal Investigator: Thomas R. Moore
Agency: NIH HD-99-001
Type: K12HD01259-04
Research Career Development Center in Reproductive Sciences
Period: September 2002-February 2007
The major goal of this project is to provide protected time and salary support for 3-5 years to junior academic faculty in a mentor-based environment that will foster the development of clinician-scientists in translational research in women's health.

"Role of Cytoplasmic $P27^{KIP1}$ in Cell Motility and Metastasis"
Principal Investigator: Cheryl C. Saenz
Mentor: Steven F. Dowdy
Agency: Rebecca and John Moores UCSD Cancer Center Mentored Translational Research Award
Period: December 2005-November 2006
This project aims to study the role of $p27^{KIP1}$ in cell motility and the relevance of its cytoplasmic localization in the development of tumor invasion and metastasis.

"Transducible Therapeutic TAT-siRNAs: Treatment of Terminal Metastatic Ovarian Cancer"
Principal Investigator: Cheryl C. Saenz
Co- Principal Investigator: Steven F. Dowdy
Agency: Rebecca and John Moores UCSD Cancer Center Collaborative Translational Research Award
Period: August 2004-July 2005
This project aims to combine protein transduction with the specificity of RNAi, to specifically kill tumor cells in terminal metastatic ovarian peritoneal carcinomatosis mouse models by targeting genes that allow these tumor cells to survive.

"Targeting of p53-activating Peptide to CXCR4 Receptor on Cancer Cells to Enhance Anti-tumor Efficacy"
Principal Investigator: Cheryl C. Saenz
Agency: UCSD Academic Senate
Period: July 2004-June 2005
The goal of this project is to enhance the delivery of anti-cancer peptides to tumor cells expressing specific receptors by linking the peptides to ligands that bind these receptors.

"Treatment of Terminal Metastatic Ovarian Carcinoma by Transducible Therapeutic siRNAs"
Principal Investigator: Cheryl C. Saenz
Agency: The Gynecologic Cancer Foundation/Florence and Marshall Schwid Ovarian Cancer Grant
Period: January 2004-December 2004
The goal of this project is to combine two recent technological advances, *in vivo* protein transduction delivery with the specificity of RNAi, to specifically kill tumor cells in ovarian peritoneal mouse models by silencing the genes that allow these tumors to escape apoptosis.

"Evaluation of Endometrial Stripe Thickness in Women with Endometrial Cancer"
Principal Investigator: Cheryl C. Saenz
Agency: UCSD Academic Senate
Period: January 2001-December 2002
The goal of this project was to determine the thickness of the endometrial stripe as measured by transvaginal ultrasound in women diagnosed with endometrial cancer.

ABSTRACTS

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Eskander R, Scanderberg D, **Saenz CC**, Yashar C. Comparison of CT and MRI cervical cancer brachytherapy target and normal tissue volumes. Oral Presentation, American Radiotherapy Annual Clinical Meeting, May 2009.

Eskander R, Grabowski J, Saenz N, **Saenz CC.** Management of 195 Benign and Malignant Ovarian Masses In a Pediatric Population: Evaluation of Operative Collaboration of Ovarian Preservation. Oral Presentation, Western Association of Gynecologic Oncologists Annual Meeting, June 2010.

Ward KK, **Saenz CC**, McHale MT, Alvarez EA, Plaxe SC. Changing Demographics of Cervical Cancer in the United States (1973-2007). Oral Poster Presentation, Society of Gynecologic Oncology Annual Meeting, March 2011.

Ballas J, Ramos GA, Warshak C, Hull A, **Saenz C**, Moore T, Resnik R. Preoperative uterine artery balloon catheters and surgical outcomes in pregnancies complicated by placenta accreta - a management paradox. Poster Presentation, Society of Maternal and Fetal Medicine Annual Meeting, February 2012.

Abbott Y, Shah N, Ward KK, McHale MT, Alvarez EA, **Saenz CC**, Plaxe SC. A program of social worker mediated introduction to psychosocial services improves patients' acceptance and access. Gynecol Oncol, 125:1, 2012.

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countries. Poster presentation, Society of Gynecologic Oncology Annual Meeting, March 2015.

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Exhibit B

MATERIALS REVIEWED AND CONSIDERED BY DR. CHERYL SAENZ

Expert Reports

1. 07/02/2021 Amended Expert Report of Daniel Clarke-Pearson, MD
2. 07/02/2021 Amended Expert Report of Judith Wolf, MD
3. 11/15/2023 Amended Rule 26 Expert Report of Daniel Clarke-Pearson, MD
4. 11/15/2023 Amended Rule 26 Expert Report of Judith Wolf, MD

Deposition Transcripts

1. 02/04/2019 Deposition Transcript of Daniel Clarke-Pearson, MD
2. 08/26/2021 Deposition Transcript of Daniel Clarke-Pearson, MD (VOL. 1)
3. 08/27/2021 Deposition Transcript of Daniel Clarke-Pearson, MD (VOL. 2)
4. 01/17/2024 Deposition Transcript of Daniel Clarke-Pearson, MD
5. 03/08/2024 Deposition Transcript of Daniel Clarke-Pearson, MD
6. 09/13/2021 Deposition Transcript of Judith Wolf, MD (VOL. 1)
7. 09/14/2021 Deposition Transcript of Judith Wolf, MD (VOL. 2)
8. 01/10/2024 Deposition Transcript of Judith Wolf, MD
9. 04/25/2024 Deposition Transcript of Judith Wolf, MD

Additional Materials

1. Saed Confidential Documents (SAED_SEPT222021_SUPPL_000001-399)
2. Saed G.M. Is there a link between talcum powder, oxidative stress, and ovarian cancer risk? 2024 May 8. doi: 10.1080/14737140.2024.2352506. Epub ahead of print.

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